To my wife, Fiona and daughter, Isabel.

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Barrett's Oesophagus and its Progression to Adenocarcinoma; A Study of Patient Profile, Diagnostic Criteria and Surveillance Practice in the U.K.

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Abstract

Background

The incidence of oesophageal adenocarcinoma has increased dramatically over the last 30 years. It is thought to be the endpoint of progression of oesophageal mucosa through Barrett's columnar-lined oesophagus (CLO) to dysplasia; a process induced by gastro-oesophageal reflux. Various patient characteristics have been attributed to the development of the disease. although evidence for specific risk factors is limited.

The diagnosis and surveillance of CLO are areas of controversy with published criteria and management protocols varying over time and between centres.

This study aimed to establish some of the patient characteristics and risk factors for progression of Barrett's, and to examine diagnostic criteria and surveillance practice in the UK.

Patients and methods

1282 patients registered with the UK Barrett's Oeosphagus Registry were studied. Data from medical records and endoscopic and histological examinations were entered onto an Access database and analysed.

Principal Results

Men were diagnosed with CLO at a significantly younger age than women and with a significantly higher frequency. Smoking was found to be a significant risk factor for development of severe dysplasia and cancer both in current and ex-smokers. Alcohol and associated *Helicobacter Pylori* infection did not significantly affect oesophageal disease severity.

Diagnostic criteria for Barrett's varied significantly over time and between centres. Surveillance was performed commonly but variably throughout the U.K. Endoscopic intervals were consistent between those centres undertaking surveillance for all grades of disease except low-grade dysplasia. Shorter intervals for surveillance of low-grade dysplasia were significantly associated with an increased detection of cancer. There was a trend towards increased survival in patients who had cancer detected as part of a surveillance programme.

Conclusions

Specific risk factors for the development of dysplasia in CLO exist. Diagnostic criteria and surveillance practice vary and have implications on further management and outcome of the disease. Early detection of dysplasia in surveillance programmes may confer some survival benefit.

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Introduction

History of Barrett's Oesophagus

In 1950 Norman R. Barrett, a surgeon from St.Thomas's Hospital, wrote a paper describing the columnar-lined oesophagus. In it he described what he called a congenitally short oesophagus with intra-thoracic gastric epithelium and congenital gastric heterotopia in the oesophagus with ulceration (1). However, his own definition of the oesophagus at the time - 'the part of the foregut, distal to the crico-pharyngeal sphincter, lined by squamous epithelium'- meant that the pathology he was actually describing was what he felt to be abnormal stomach rather than abnormal oesophagus. His views had changed by 1957, however, when he described the changes at the lower end of the oesophagus as 'neither true stomach nor oesophagus' (2).

All of his descriptions assumed that the condition was congenital, with the pathogenesis being one of failure of the embryonic lining of the gut to achieve normal maturity; a view echoed by others at that time (3) (4).

In 1953, Allison and Johnstone (4) pointed out that the columnar epithelium Barrett was referring to was of so-called *cardiac type*; ie. did not secrete digestive enzymes and was therefore not strictly gastric. They also suggested that two conditions occurred; one, a condition where stomach musculature and peritoneum were present in the chest – so called 'thoracic stomach'; and one where no peritoneum but where gastric mucosa was present in the oesophagus – so called oesophagus lined with gastric mucous membrane.

Perhaps the first people to reject the congenital theory and to make the assumption that these changes in the lower oesophagus were acquired secondary to reflux were Moersch, Ellis and McDonald in 1959 (5).

In 1960, Hayward (6) defined the oesophagus - and particularly the cardia region - clearly for probably the first time. He coined the term 'junctional epithelium' and suggested his new definitions should have an impact on future classification of gastric and oesophageal carcinoma, as well as the aetio-pathogenesis of lower oesophageal reflux disease. He agreed with Moersch and others in rejecting a congenital theory to explain the presence of columnar epithelium in the lower oesophagus and believed that what he was seeing was a metaplastic change from

squamous to junctional epithelium as a result of the chemical insult of gastro-oesophageal reflux.
This view has largely persisted until the present day, although, the precise mechanism of this reflux-induced metaplastic change and the exact anatomy of the lower oesophageal region is still not clearly understood, and interest and research into this area is still extensive. Since Barrett did not describe what we understand today as columnar-lined oesophagus (CLO), this latter descriptive title for the entity has attracted support.

Anatomy/Embryology

In order to understand the anatomy of the oesopahgus, both on a gross structural and histological level it is useful to appreciate its embryological origins.
The primitive gut is formed as a result of cephalocaudal and lateral folding of the embryo, incorporating a portion of the endoderm-lined yolk sac cavity in the process to form a blind ending tube.
The foregut develops from the cephalic part of the primitive gut in conjunction with development of the pharyngeal gut or pharynx. At about four weeks gestation the 'respiratory diverticulum' or 'lung bud' appears at the ventral wall of the foregut at the border with the pharyngeal gut. This gradually separates from the dorsal part of the foregut through a partition known as the esophagotracheal septum.
The foregut is thus divided into a ventral portion – the respiratory primordium, and a dorsal portion – the oesophagus.
Initially the oesophagus is short, but lengthens as the heart and lungs develop. Failure of this lengthening may result in a congenital hiatus hernia. Failure of canalisation results in oesophageal atresia and persistence of communication with the respiratory system results in tracheo-oesophageal fistula.

In his book entitled *'The esophagus'* (7) Donald O. Castell summarises the structure and function of the oesophagus succinctly;

" ...The esophagus is the simplest of organs, a hollow muscular tube with a sphincter at each end, designed to keep itself empty in the face of frequent intrusions from above and below."

However, it has taken many people many years to attempt to explain the precise anatomy of the oesophagus, its histological makeup and how it goes about maintaining its normal physiological functions. Even today the exact neuro-endocrinological-anatomical synergisms are not truly understood, and the mechanisms of failure of oesophageal physiology, so important in understanding the process of disease, are still under extensive investigation.

The precise definition of the oesophagus; where it starts and ends; its cellular lining and consequent clinical significance has been debated for many years.
In his 1960 paper in *Thorax,* John Hayward (6) underlined the confusion existing at that time over a precise anatomical and histological definition of the oesophagus, and the clinical implications that arise from this.
He firstly pointed out that the oesophagus must be regarded as a tube that starts from the throat and ends in the stomach; perhaps an oversimplified definition, but one that forces the recognition of the entire oesophagus and the underlying cellular lining that this entails. His point was that many before him (including Barrett) defined the oesophagus as a tube lined purely by squamous epithelium; therefore not including the part below the squamo-columnar junction (SCJ) as belonging to the oesophagus at all. From the outside the oesophagus clearly ends at the gastro-oesophageal junction (GOJ); that point at which it enters the stomach, and some 1 to 2 cm lower than the SCJ. He was therefore clear to define the oesophagus as a tube lined by both squamous *and* columnar epithelium.
He also classified the columnar epithelium at the lower end of the oesophagus – and extending a few centimetres into the stomach – as a *'junctional type epithelium'*, being unlike normal gastric epithelium in that it does not possess the ability to secrete digestive enzymes, but does offer protection from gastric acid exposure – a so called *'buffer zone'*.

He also defined the cardia precisely for, perhaps, the first time – another anatomical region of some debate – as the 'sphincteric lower part of the oesophagus between the insertion of the phreno-oesophageal ligament and the gastro-oesophageal junction.'

Modern definitions generally describe the oesophagus as extending from the cricoid cartilage to the cadiac orifice of the stomach, projecting through the diaphragm at the level of the seventh costal cartilage. The lower limit has been defined as the part where it enters the stomach and is identifiable macroscopically (and endoscopically) by the flaring of the stomach and the gastric rugal folds. Structurally, the oesophagus is made up of an outer layer of longitudinal muscle and an inner, circular, muscle layer. Within these muscular layers exist two autonomic nerve plexuses - the myenteric (Auerbach's) plexus situated in between the outer and inner muscles, and the submucosal (Meissner's) plexus situated between the muscularis mucosa and the circular muscle. The nature of the muscular fibres of the oesophagus vary along its length with the proximal 5% consisting of striated muscle, the lower 50-60% smooth muscle and the middle 35-40% consisting of a mixture of both types.
Normal physiological peristalsis of the oesophagus relies on a complex interaction between motor nervous and autonomic nervous function acting on these various muscle types.
The two sphincters that Castell mentions make up an important part of the structure of the oesophagus and much research has been targeted towards their role in the maintenance of normal physiological function, with particular emphasis recently on the one at the distal end of the oesophagus; the so-called *lower oesophageal sphincter* (LOS).

The upper oesophageal sphincter (UOS)
The sphincter at the upper or proximal end of the oesophagus – also known as the *pharyngo-oesophageal sphincter* – functions as part of both the pharynx and the oesophagus. There is a large contribution from the cricopharyngeal muscle under

motor nervous supply from the pharyngeal branch of the vagus (8) (9).
Swallowing is associated with inhibition of motor nerve activity supplying the UOS and subsequent relaxation of the sphincter (10) (11) (12) (13) resulting in sphincter opening. It has been demonstrated that the length of time of opening and the size of the opening depends to a certain extent on the size of the food bolus and on intrabolus pressure.
During belching, the UOS relaxes – which is a prolonged relaxation associated with the absence of pharyngeal contraction.

The lower oesophageal sphincter (LOS)
The LOS was initially thought to be purely a physiological sphincter with no corresponding structurally specialised anatomy (14). Moersch and others, over 50 years ago, did not recognise any structural change in the muscular wall of the oesophagus deep to the submucosa at the GOJ, and subsequently noted that it was the peritoneal attachment that marked the locus of the junction externally (5). However, various anatomical factors have been described since then which seem to play a role in sphincter function.
As previously mentioned, the oesophageal muscular wall consists of skeletal muscle fibre types in roughly the upper third, visceral type fibres in the lower third and mixed in between. There is no sharp line of demarcation between the muscle types.
The distal 5cm or so constitutes the LOS.
Liebermann-Meffert et al (15) described the LOS as a ring of muscle angling obliquely upwards from the lesser to the greater curvature of the stomach. They suggested that this ring is split into two segments one; a segment consisting of short transverse muscles clasping around the oesophagus and two; long oblique loops of muscle stretching towards the stomach.
There is also a well documented contribution from the right crus of the diaphragm, the fibres of which arise - together with the left crus - from the bodies of the upper lumbar vertebrae alongside the psoas muscle. They then pass to the

left of the diaphragmatic opening and help to maintain a constant angle between the oesophagus and the stomach.

Macroscopically, there does not appear to be any obvious thickening of the oesophageal musculature itself around the LOS, however, it has been shown more recently that on microscopic examination the number and types of myosin filaments here are different from the rest of the oesophageal body (16).
The smooth muscle cells of the inner circular muscle of the sphincter are dense with nerve fibres staining positive for NADPH diaphorase and have been shown to respond to electrical stimulation via a NANC (non adrenergic non cholinergic) pathway mediated via products generated from L-arginine (17).

Stomach
Understanding the precise anatomy of the stomach has obvious implications on defining the oesophagus accurately.
The stomach is the part of the foregut that extends from the gastro-oesophageal junction to the pyloric antrum and consists histologically of three distinct regions – the cardia, body and antrum.
Throughout the whole of the stomach, columnar mucus-secreting epithelium lines the surface of the gastric mucosa and produces a viscid gel known as the *gastric mucosal barrier.* The surface epithelial cells also secrete bicarbonate and sodium ions which diffuse into the gel and help to buffer hydrogen ions entering form the gastric lumen. This allows a pH gradient to exist from 1 to 2 at the luminal surface to neutrality at the plasma membrane of the epithelium.
Other specific cells involved in acid and hormonal production make-up the mucosa in varying proportions throughout the stomach.

The precise definition of the cardia and gastro-oesophageal junction (GOJ) has sparked much controversy over the years. From the early descriptions by Allison, Johnstone, Hayward and others, right up to the present day, exact macroscopic and histological landmarks of these regions have proved hard to define.

Previously, many have defined the GOJ anatomically simply as the proximal limit of the rugal folds. In the British Society of Gastroenterology (BSG) guidelines (18) for the management of Barrett's columnar-lined oesophagus, the GOJ is defined more precisely as the '*....confluence of the proximal limit of longitudinal gastric folds, the distal limit of linear oesophageal vessels and the point of flaring of the stomach from the tubular oesophagus when the lumen is deflated.*' A recent definition by Odze (19) describes the 'true gastric cardia' as the region between the proximal limits of rugal folds and the histologically defined gastric oxyntic mucosa; the area being lined by either cardiac or oxyntocardiac mucosa. Therefore it is only oesophagus if it is proximal to the proximal limit of rugal folds. Chandrasoma's (20) recent definition of the GOJ disputes this by stressing that if submucosal glands can be demonstrated histologically then this, by definition, must be oesophagus – submucosal glands are thought not to exist in the stomach (21). In their recent study on cadaveric oesophageal specimens they found that submucosal gland could exist beneath cardiac and oxyntocardiac mucosa and thus areas that Odze would describe as cardia they would argue were metaplastic columnar-lined oesophagus resulting from reflux. Chandrasoma concludes by defining the GOJ as '*..the proximal limit of gastric oxyntic mucosa as defined by histology*'.

The gastric body mucosa lines the proximal two-thirds of the stomach and consists of tightly-packed tubular glands with acid and intrinsic factor-secreting parietal (or oxyntic) cells in the upper parts and enzyme secreting chief cells in the lower parts. The mucosa also contains neck cells (at the bases of the gastric pits) - which provide the stem cells for the mucosa - and endocrine (enterochromaffin-like cells), which are involved in the mediation of parietal cell activity.

The antral mucosa extends from about one third of the distance along the lesser curve to the pylorus in a roughly triangular distribution. The antral glands are morphologically different from those of the gastric body being more branched, tortuous and less tightly-packed. Antral mucosa contains dense endocrine but fairly few and scattered parietal cells. Endocrine cells include G cells – which

secrete gastrin and are the most densely packed; D cells – which secrete somatostatin; EC cells – which secrete 5-hydroxytryptamine (5-HT); P cells – which secrete bombesin and S cells which secrete secretin.

Histology

Histologically, the oesophagus is made up of four main layers. The mucosa, the submucosa, the muscularis propria and the adventitia.

The mucosa

The mucosa is lined by non-keratinizing stratified squamous epithelium; comprising of a basal, intermediate (prickle cell) and superficial layer (22).
The basal layer is only two to three cells thick and forms the proliferative compartment from where cells migrate upwards, mature and desquamate at the surface.
The epithelial layer is predominantly structured by superficial and intermediate squamous cells arranged in cohesive sheets, small clusters and as single cells.
Morphologically the superficial squamous cells appear as large, flat, polygonal cells with abundant, often transparent cytoplasm and a single, centrally located round nucleus.
The intermediate squamous cells have a similar appearance but are a little smaller than the superficial ones and have denser cytoplasm and larger nuclei.

The submucosa

The submucosa consists of relatively hypocellular, dense, collagenous and elastic tissue; through which courses blood vessels, lymphatics and nerves. Within the lamina propria and submucosa are variable numbers of mucus-secreting glands which connect with the surface via ducts lined by a single layer of columnar and cuboidal epithelial cells.

The muscularis propria

This layer consists of skeletal muscle fibres in roughly the upper third; smooth muscle fibres in the lower third and mixed inbetween. Between an inner and outer layer lies the autonomic plexi.

The adventitial layer

This is loose connective tissue that blends with the surrounding mediastinal soft tissues.

An understanding of the embryological origins of the oesophagus arose from much work done in the early part of the 20th century. In 1952, Johns (23) re-examined some of this evidence in light of his own work done examining serial embryological sections, and produced a paper summarising much of the early histological development of the oesophagus, including some new theories disputing some of these older observations. The initial embryological stage in development of the oesophagus - after differentiation from the rest of the foregut – is thought to be generalised cellular proliferation and stratification of the epithelial lining. Johns showed that the epithelium starts as stratified columnar which then goes through a two-layered to a multi-layered stage over the early weeks of development. Earlier theories suggesting that the lumen then becomes obliterated and 're-opened' via a process of vacuolation were disputed by Johns who felt that complete obliteration did not occur, though recognised the presence of vacuoles in specific areas in the oesophagus.

Johns then described patches of ciliated cells arising from the middle-third of the oesophagus (from underlying deeper cells) and spreading upwards and downwards to form a complete epithelial lining.

The stratified columnar epithelium then becomes replaced by a stratified squamous lining, originating and spreading in a similar fashion.

Areas of tall columnar cells make their first appearance at the upper and lower ends of the oesophagus and become the superficial oesophageal glands. Frequency of persistence of these glands into adulthood is controversial and many regard their presence to be heterotopic gastric mucosa; and as they can – in theory – produce acid and pepsin, it is thought they may lead to localised area of ulceration or stricturing. The superficial glands develop slightly earlier than the deep glands which only appear once the epithelium is fully stratified squamous

and tend to develop largely in the post-natal foetal stages. Their presence is a much more frequent finding in the adult oesophagus.

Physiology/pathophysiology

The neurophysiology of the oesophagus is complex and it is vital that it functions normally in order for swallowing to occur properly and for the prevention of gastro-oesophageal reflux.

Normal oesophageal motor function consists of co-ordinated peristaltic waves (swallowing), transient lower oesophageal relaxations (TLOSRs) and a degree of LOS tone. The peristaltic reflex consists of two components; an ascending contraction above and a descending relaxation below the site of distension. Recognition of the LOS as a discrete anatomical and physiological structure has been prevalent for the last 20-30 years, however, the recent increase in gastro-oesophageal reflux disease (GORD) has led to a resurgence of research into this area.

The resting tone of the sphincter varies from 10-30mmHg and is affected by several intrinsic and extrinsic factors including intra-abdominal pressure, gastric distension, peptide hormones, various foods and many drugs.

Intrinsically, it has been shown to have a lower resting membrane potential than adjacent circular muscle (24) (25), exhibit an increased passive permeability to potassium ions (26) and have a higher intrasystolic concentration of calcium ions (27). It has been postulated that sphincter control may be maintained by inositol-phosphate mediated continuous release of calcium ions.

Neurogenic control of the sphincter (via the autonomic myenteric plexus) has been demonstrated to arise from pre-ganglionic motor neurones localised in the dorsal motor nucleus (DMV) of the vagus; with the caudal DMV evoking LOS relaxation and the rostral DMV, LOS contraction (28). The autonomic pathway is sensitive to various factors including gastric distension and several hormones. Cholecystokinin (CCK) has been shown to cause a significant reduction in LOS pressure, with no affect on TLOSRs (29). Endogenous Gastrin levels seem to provide an important stimulus to the rise in LOS pressure after food, with poor

gastrin responses resulting in only small pressure rises and subsequent gastroesophageal reflux (30). In order for a food bolus to pass through into the stomach the LOS must temporarily relax; however, increase in frequency of this relaxation may be a significant contributing factor to GORD.

There are a number of factors specifically affecting TLOSRs.

Degree of proximal gastric distension has been shown to have a direct relationship with rate of TLOSRs (31). Stage of sleep has also been demonstrated to have an effect; where secondary contractions seem to be increased during the REM phase of sleep (32).

As well as increase in TLOSR frequency, loss of tone in the LOS may also be associated with GORD and there are a number of factors thought to be directly related to this.

Table 1 summarises some of these factors.

Table 1

Factors associated with LOS and reflux

Factor	Author	Summary
Fatty foods	Holloway (33)	Aggravates reflux in patients with GORD
Age	Ferriolli (34)	Abnormal oesophageal motility increases with age
Alcohol	Grande (35)	Increases oesophageal dysmotility
Coeliac disease	Usai (36)	Commonly have abnormal oesophageal motility
NO synthase	Mearin (37)	Absent in myenteric plexus of GOJ in patients with achalasia
Sleep patterns	Castiglione (32)	Affect oesophageal motor activity (increased in REM)
Prostaglandins	Cagossi (38)	Inhibit LOS function
Smoking	Kahrilas (39)	Lowers LOS pressure (chronic), increases acid reflux events acutely
Gastrin (endogenous)	Henderson (40)	Not a physiological determinant of LOS
DM	Stewart (41)	Leads to decreased LOS pressures via autonomic neuropathy
CCK (exogenous)	Ledeboer (29)	Reduces LOS pressure but no affect on TLOSRs or acid exposure
Gastric distension	Scheffer (31)	Directly related to rate of TLOSRs
5 HT	Pehlivanov (42)	Agonists (cisapride) decreases TLOSRs and increases LOS pressure in sleep
H Pylori	Wu (43)	Enhances oesophageal dysmotility and LOS dysfunction

There are a number of specific conditions that affect the neuro-anatomical function of the oesophagus that may result in abnormal LOS tone and malcoordination of oesophageal peristalisis (a condition known as achalasia). For example, fibrosis and atrophy of smooth muscle cells occur in systemic sclerosis and lead to dysphagia. In Chaga's disease, destruction and degeneration of intrinsic nerves result from this neurotropic infection and have a similar clinical effect.

Idiopathic achalasia is a relatively uncommon condition, the aetiology and pathogenesis of which is largely unknown. However, studies have shown a T-lymphocyte predominant inflammatory infiltrate present along the nerve fascicles and around ganglion cells in oesophageal specimens in a significant number of cases of achalasia, suggesting that a probable inflammatory reaction - possibly of autoimmune origin - may be implicated (44).

Hiatus hernia

Perhaps the most common anatomical/mechanical disorder of the oesophagus is a hiatus hernia (HH). This is simply defined as the presence of part of the stomach above the diaphragmatic orifice and, although formerly thought to have arisen from congenital shortening of the oesophagus, is now thought to be an acquired condition. Some studies have shown that patients with CLO have a 90% chance of having an associated hiatus hernia (45).

2 case controlled studies with multi-variate analysis have shown that presence of a hiatus hernia is a risk factor for development of oesophageal adenocarcinoma (AC), with risk being proportional to HH length (46) (47).

Inflammatory disorders

Acute oesophagitis is usually of only minor clinical importance with the majority of infections representing spread of bacteria from the nasopharynx. The majority of oesophageal inflammation seen in the clinical setting tends to be of a more chronic nature and is usually not related to any specific infecting organism – so called 'non-specific chronic oesophagitis'. The pathogenesis of this inflammation is thought to be via reflux of gastro-duodenal contents into the oesophagus in the majority of cases and gives rise to the term 'reflux oesophagitis'.

Gastro-oesophageal reflux disease (GORD)

Gastro-oesophageal reflux disease (GORD) is a condition that arises as a result of gastric contents entering the oesophagus (Gastro-oesophageal reflux (GOR)) leading to symptoms and often the development of mucosal lesions. Symptoms

may vary but include heartburn, abdominal and/or retrosternal pain, acid brash, belching, nausea and vomiting. The frequency of these types of symptoms within the western population is relatively high, with US surveys over the last 15 years showing that up to 44% of people experience heartburn at least once a month (48) (49). The point at which the condition should be defined as full GORD is not clear, however, but is usually based on severity of symptoms, impact on quality of life and/or extent of oesophageal mucosal damage.

The reason why some patients with GORD symptoms develop mucosal lesions and some do not is not fully understood, but may be due to length of oesophageal exposure to gastric contents, toxicity of the refluxate and sensitivity of the tissue itself (50) (51).

The pathophysiology of GORD is most likely multi-factorial, but is thought by many to be primarily a defect in motility of the oesophagus and lower oesophageal sphincter, often combined with a delay in gastric emptying (52) (53) (54).

Mechanisms of GORD

There are many factors thought to predisopse to gastro-oesophageal reflux and there is a logical overlap with the factors found to affect LOS physiology as mentioned earlier.

The LOS can be thought of as an anatomical/physiological sphincter with both intrinsic and extrinsic components playing a role in maintaining a so called 'high pressure zone' (HPZ) that acts to prevent reflux of gastric contents up into the oesophagus. Some of the intrinsic mechanisms - and factors affecting their function - have already been mentioned.

The extrinsic/anatomical factors can largely be divided into two groups: factors involved in a 'flap-valve' mechanism at the junction - and factors affecting distal oesophageal compression. The flap-valve mechanism is largely comprised by the natural cardio-oesophgeal angle, the 'pinchcock' affect of the diaphragmatic crural fibres and the 'mucosal rosette' (natural folds in the mucosa at the junction). Distal oesophageal compression is maintained by the presence of the

phreno-oesophageal ligament and by transmitted abdominal pressure. All of these extrinsic factors may be affected by the presence of a hiatus hernia and it is not surprising, therefore, that it is a frequent finding in people suffering with gastro-oesophageal reflux.

High intake of fatty ('fast') food may well be involved in the development of GORD and almost certainly plays a role in explaining the high prevalence of the disease in western populations and the vast increase over the last 20-30 years (55) (56). A high Body Mass Index (BMI), something that has also shown an increasing trend in western societies over the last few decades, and consumption of specific alcoholic beverages such as white wine have also been shown to have an affect on development and severity of GORD (57) (58).

Histological changes in reflux oesophagitis

The presence of gastro-duodenal contents in the oesophagus causes an inflammatory reaction with a resulting degree of cellular damage.

The basic inflammatory response consists of an epithelial reaction associated with a conventional inflammatory cell reaction; however much work has looked at the specific changes that occur in order to improve accuracy in diagnosis of the disorder.

Characteristic macroscopic tissue changes secondary to reflux include; mucosal oedema, erythema and haemorrhage and necrosis and sloughing of superficial epithelium in prolonged severe cases. Microscopic changes reflect the direct reaction of the oesophageal lining to chemical injury as well as a compensatory cellular proliferation that arises as a result of the subsequent desquammation – a phenomenon that is observed in the basal layer of the epithelium (basal cell hyperplasia).

Ismail-Beigi (22) showed this epithelial hyperplasia – as manifest by basal cell thickening and papillary elongation – to be one of the earliest histological changes in reflux disease. However, the specificity of these changes to GORD is unclear and others have not been able to confirm these findings (59) (60). In a study done

by Weinsten et al (61) they found seventeen out of nineteen asymptomatic patients to have epithelial hyperplasia at biopsy.

Other changes that are thought to be specific to reflux oesophagitis include balloon cell formation (a very sensitive marker of early injury to oesophageal mucosa) (62) and intraepithelial leukocytosis (63) (64) (65).
The presence of acute inflammatory cell infiltrates (neutrophil leukocytosis) have been shown to be specific but not very sensitive markers of GORD (66). Other non-specific changes present in reflux oesophagitis include epithelial reparative (or regenerative) atypia, the clinical significance of which has not truly been established. Various other markers for reflux oesophagitis have been looked at in order to aid in the diagnosis of the disease. Ismail-Beigi et al (22) demonstrated that by measuring basal cell zone thickness and papillary height of squamous epithelium the presence of reflux oesophagitis can be diagnosed in the absence of inflammatory cell infiltrates.

Clark et al found the presence of *carditis* to be a frequent finding on biopsies taken distal to the SCJ in patients with clinical reflux (67). However other authors have not agreed with these results, relating the presence of carditis to inflammation associated elsewhere in the stomach and particularly to the presence of *Helicobacter pylori* infection (68).

Aetiology of CLO
Chronic exposure of squamous mucosa to refluxed gastric contents leads to accelerated desquammation and proliferation of the basal layer of the epithelium as described above.
The cellular regeneration of epithelial tissue in the process of healing may restore continuity to the lining of the oesophagus, however, the associated fibrosis that occurs occasionally leads to the formation of segmental narrowing or strictures; a condition that can have serious clinical sequelae.

Although restoration of epithelial continuity may be achieved by proliferation of squamous cells, occasionally this is not the case and columnar cells provide the new epithelial lining. This process is thought to be the basis behind the pathogenesis of CLO; although many theories exist as to the precise mechanisms by which this occurs. Historically, there has been much debate as to how these columnar cells arise and three main theories now exist:

1. transdifferentiation of stem cells
2. migration of submucosal glands
3. colonisation of gastric cells to damaged squamous mucosa

In 1976, Paull (69) described 3 distinct types of columnar mucosa which he thought could be seen in, and were diagnostic for CLO.

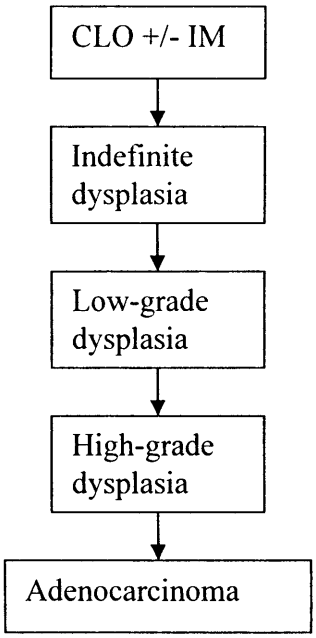
1. a junctional type resembling normal gastric cardia
2. an atrophic fundal type containing scanty specialised gastric secretory cells
3. a 'specialised' mucosa in which the epithelium is undergoing a further metaplastic change toward an intestinal type and has acquired goblet cells.

These histological observations became the hallmark of CLO by which future histological diagnoses would be made.

There have been several studies that have demonstrated - in aetiological terms - that the development of CLO is a step along the spectrum of oesophageal disease that begins with oesophagitis. Patients with CLO have been shown to have a higher proportion of LOS dysfunction and general peristaltic abnormalities when compared to patients with uncomplicated oesophagitis and over 90% have an associated HH (45). CLO is also associated with a higher level of acid exposure and exposure to duodenal content (70) (71).

The presence of metaplastic cells in CLO – so called intestinal metaplasia (IM) – has been shown to be a pre-malignant condition (72). A number of studies on the natural history of CLO have suggested an increasing risk of adenocarcinoma as the epithelium progresses through various stages of dysplasia (73) (74) (75) (see Figure 1) and the pathway is modelled on the multi-step pathway of carcinogenesis (76).

Figure 1 Flowchart showing pathway of progression from CLO to AC



The time taken to progress through these stages is not entirely known – and has proved very hard to assess accurately. Some authors have demonstrated development of AC from CLO to occur at between 1in 52 (77) and 1 in 75 patient years (78) (79) (80) (81) (82) although there has been some criticism recently that these reports may overestimate rates of progression of AC, particularly as a consequence of publication bias, and the true risk may be in the order of 1 in 200 (83).

On a micro-pathological level, the aetio-pathogenesis of these steps has been demonstrated in more detail.

Angiogenesis is a fundamental stage in the development of all organs (84). The process has also been been described to be essential in tumour growth and metastasis (85) and has been included in one of the six hallmarks of cancer progression in CLO (86).

Studies have shown an increased microvascular density, aberrant neovasculature, and a higher level of expression of vascular endothelial growth factor A (VEGF-A) in non-neoplastic Barrett's epithelium with an increase in these observations as the epithelium progresses through various stages of dysplasia to cancer (87) (88) (89). The expression of lymphangiogenic growth factor (VEGF-C) has also been shown to increase as the epithelium passes through these various stages (88).

Treatment

The treatment of CLO is largely preventative reflux therapy. Whether by pharmacological or surgical means, the aim is to decrease oesophageal exposure to gastro-duodenal refluxate and to allow healing of the mucosa with time. Regression of CLO has been demonstrated both in response to medical (90) and surgical intervention (91) although complete circumferential regression has rarely been reported. Reversal of dysplasia has been reported – although diagnostic inaccuracies of this stage of the disease may make evidence for this slightly more unreliable *(see diagnosis of CLO introduction)* and there are reviews of evidence that dispute these findings (92).

Traditional pharmacological intervention is aimed either at simple neutralization of the acidic gastric contents (eg. bicarbonates); to cause an increase in stomach and small bowel motility/emptying (so called 'pro-kinetic' agents such as *domperidone*) - or in reduction of gastric acid output; either via inhibition of the proton pump mechanism, (eg. *omeprazole*), or in blocking of histamine receptors (eg *ranitidine*).

Surgically, either anatomical correction of hiatal herniae, and/or tightening of the GOJ by one of the various types of fundoplication have been the mainstay in anti-reflux procedures. Variations in techniques in order to achieve this exist and evidence for their varying efficacy has been extensively debated over time. Some studies have suggested a greater degree of symptom control and healing of associated strictures in patients treated surgically over medical therapy alone (93) (94); and although disease regression seems to be more commonly reported after

anti-reflux surgery it only appears to occur in 10-44% of patients overall (93) (95) (91).

Endoscopic ablation of the affected oesophageal mucosa is a relatively new treatment modality which is used in a number of specialized centres throughout the U.K. It encompasses a number of techniques; either using Nd-YAG, GaAIAs or Argon plasma coagulation LASER devices. Photodynamic therapy involves sensitization of the oesophageal mucosa with a photosensitive agent such as 5 aminolaevulinic acid and then exposure of the patient to light of a specific wavelength and has been shown to have varying degrees of success in treating Barrett's metaplasia and dysplasia (96).

Newer therapies have been developed in order to halt the progression of Barrett's mucosa through grades of dysplasia and include drugs designed to stop the process at various levels of carcinogenesis.
Angiogenesis has been shown to be an important factor in the progression of CLO through to AC (84) and some therapy has been aimed at this stage in the pathogenesis . COX 2 inhibitors have not only been shown to have some effect on apoptosis and cell proliferation but also on angiogenesis (97).
The currently unpublished AspECT (Aspirin Esomeprazole Chemoprevention) Trial, run by the Oxford Clinical Trials Consortium in The U.K., aims to look at the effect of esomeprazole and aspirin on the development of AC in patients with established CLO.

Patient demographics/characteristics

Incidence of CLO/AC

The incidence of CLO has been rising in Europe and North America over the last 20-30 years (98); however, in the USA this observed increase seems to parallel the increase in the number of upper gastrointestinal endoscopies (99), whereas, in the UK, there appears to have been a real increase which is above and beyond the increase in rates of endoscopy observed (100) (101) (102). This rise in incidence of CLO has coincided with a dramatic rise in incidence of oesophageal adenocarinoma. Whereas 20 years ago the vast majority of oesophageal cancer was thought to have consisted of squamous cell types (>90%) (103) the ratio of SCC to AC is now probably more like 75:25 and it is now the cancer with the most rapidly increasing incidence in the Western world (104) (105) (106)

In Northern and Western Europe and North America; between 1976-1978 the average annual age-adjusted incidence of oesophageal adenocarcinoma in white males was 0.8 per 100,000; whereas between 1988 and 1990 this had increased to 2.5 per 100,000 (107).

The precise prevalence or incidence of CLO is difficult to assess accurately. For a start, comparison of prevalence rates across study populations requires a constant definition of CLO. It also depends on populations used as the denominator, diagnostic techniques and may be affected by varying 'care-seeking behaviour patterns' of patients from different geographical, social and cultural backgrounds (108).

20 years ago the incidence of CLO in patients having endoscopic examinations for assessment of oesophagitis was quoted at between 8 and 20 percent (109) (110) (111) (112) and 44% of patients with chronic oesophageal strictures (113)

More recent studies have shown a prevalence estimation of between 0.8% to 3.9% in patients undergoing upper GI endoscopy for all reasons (114) and approximately 3% to 30% in patients being investigated for GORD (115) (116) (117) (118) (119)

In a clinical and autopsy study performed in the USA in 1990, the incidence of CLO at endoscopy was found to be 18 per 100,000 population, whereas at autopsy

the corresponding figure was 376 per 100,000, with only 5% becoming clinically apparent (99). The incidence of AC has also escalated over a similar timeframe; and has in fact increased eightfold in Western Europe in the last 3 decades; a rate of increase greater than that of any other solid tumour (104) (120). Before this observed vast increase in incidence of AC this type of oesophageal tumour made up less than 10% of all oesophageal tumours – the most common being squamous cell carcinoma (SCC) – whereas now it represents over 70% of oesophageal tumours in most UK units (121).

Risk of progression to AC

CLO and GORD are the only known precursors of AC (82) (122) (123). It is thought that between 5-10% of patients with CLO will develop AC; the annual risk in surveillance programmes being 0.5-1%, which is 30-125 times that of the general population (104) (79) (124) (78) (77) (125) (126). For every 100,000 cases of CLO, 500 will develop annually into AC (127) – which exceeds the risk of lung cancer in an individual who has smoked one pack of cigarettes per day for 20 years (128).

In the UKBOR analysis of 5317 CLO cases in the UK, fewer than 5% developed AC (129); approximately 80% of these were prevalent ACs (ie cancer arising within 1 year of CLO diagnosis) and 20% incident.

The rate at which CLO progresses through increasingly severe dysplasia to AC has been quoted at between 1 in 44 and 1 in 441 patient years (81) (82). This is 30-125 times the rate of AC development in the general population (130).

A number of Eurpean studies have shown the mean age for the diagnosis of CLO to be just over 60 years in men (131) (132) (133;134) and approximately a decade older for women. Prevalence appears to increase with age to a maximum at age 70-79 years, of 4.89% in males and 3.75% in females (135). It has been postulated that pre-menopausal women may be protected to a degree by their hormones and this may explain the delay in onset of the disease and the slightly slower rise in prevalence with age seen in females (135).

The effect of alcohol and smoking on development of CLO and progression to dysplastic disease is controversial. Alcohol consumption and tobacco use do not appear to play a role in the development of CLO in a number of studies (136) (137), nor in the development of AC (138). However, a number of authors have found a positive association with the development of dysplastic disease in patients with established CLO (137) and in the development of AC per se (139) with smoking and alcohol intake, with some studies showing a dose-dependent risk of AC development with cigarette smoking (140).

In a study done by Vaughan et al, the population attributable risks for AC– although less than for SCC – was found to be 34% for tobacco and 10% for alcohol (141).

Some studies have shown that the type of alcohol may be relevant with consumption of spirits ('hard liquor') associated with longer lengths of CLO – with no such association found with wine or beer drinking (142).

A BMI of 30 or more is generally considered to be obese, and in the U.K. 11% of men and 13% of women fulfil this criterion (143).

Several series have shown obesity to be a risk factor for the development of AC with some studies showing an odds ratio of 3.0 for patients in the 4^{th} quartile of the BMI range (144) (145). In a study by Caygill et al (136) a high number of patients with CLO who were younger than 50 were clinically obese (almost 3 times that of the normal population) although in the older age groups there did not seem to be the same association; and they therefore conclude by suggesting that obesity may well be a significant risk factor for the development of CLO in younger people.

Dietary studies have shown conflicting evidence for risk of CLO and AC development. Various specific dietary factors may affect LOS pressure – including fats, chocolate, alcohol, coffee and tea as may more general dietary habits such as total caloric intake, meal size, frequency of eating and obesity (146); although the strength of association of these factors with development of mucosal pathology is controversial. Some studies have postulated that dietary nitrates may also be a direct risk factor for AC development (147)

Diagnosis of CLO

Historically, the precise definition of the anatomy of the oesophagus and especially its histological makeup has been extensively debated. This has had obvious implications for the recognition and diagnosis of various oesophageal pathologies and their subsequent management.

In Barrett's 1950 seminal paper on peptic ulceration and oesophagitis (1) he initially felt that the presence of columnar epithelium in the lower oesophagus was in fact anatomically part of the stomach and not oesophagus at all, and it wasn't until further studies by other authors (4) (6) that the concept of the oesophagus *lined* by this type of epithelium was developed.

In 1983, Skinner et al suggested that the diagnosis of Barrett's be confined to a columnar lined oesophagus (CLO) of at least 3cm in length (148). This measurement largely arose as a way to facilitate ease of diagnosis (and essentially to prevent over-diagnosis) at endoscopy without confusing the presence of normal gastric mucosa, or normal columnar lining of the gastric cardia, with pathological oesophageal changes. Since then, the presence of a minimal length of columnar-lined lower oesophagus necessary to fulfil the criteria for a diagnosis of CLO has varied anywhere from 2 to 5 cm.

In 1994, Spechler et al demonstrated a high prevalence of specialised columnar epithelium – a condition with suspected malignant potential – at the GOJ in symptomatic patients with endoscopically absent CLO (149). This has subsequently been referred to as 'ultra-short segment Barrett's, and hightened awareness to the importance of recognition of short segment disease as a possible pre-malignant condition.

However the significance of finding IM at a normally positioned SCJ has been debated.

Hackeleberger et al, found that in patients with a *normally* positioned SCJ, 13.4% had IM just below the SCJ, and that this was significantly associated with gastric intestinal metaplasia and gastric H Pylori infection (150).

Goldblum et al also found that IM at the cardia was present as often in controls as in patients with a diagnosis of GORD and was also significantly associated with HP infection (151).

Whether the presence of specialised columnar epithelium indicates an increased risk of cancer regardless of its precise location within the gastro-oesopahageal junction or not remains controversial.

Morphology of CLO

The actual morphology of the Barrett's segment itself has undergone various interpretations as to the significance with regards to pathological potential. Traditionally CLO was defined as only circumferential segments of columnar-lined epithelium. More recently, however, the presence of 'tongues' of CLO (non-confluent Barrett's) have been included in the spectrum of diagnosis and malignant potential in disease with this morphology has been demonstrated (152).

Histology

In 1976, Paull et al described three types of histological change relating to CLO (69):

An area of normal fundal mucosa - without the glandular density - arising next to the gastric mucosa; above this an area of mucosa resembling a junctional gastric type; with the absence of chief, parietal, Paneth and goblet cells; and above this (next to squamous cells of the oesophagus) an area of usually incomplete intestinal metaplasia or specialised intestinal metaplasia with villi and goblet cells present but without the presence of a well defined brush border.

Since then the presence of goblet cells have been paramount for the diagnosis of IM, and staining with H&E-Alcian blue at pH 2.5 is the recommended technique for both sensitive and specific interpretation of this (153).

The malignant potential of IM in the context of the columnar-lined oesophagus was first clearly described by Spechler et al in 1996 (72).

Endoscopic diagnosis

The use of contrast radiology to diagnose CLO has proven to be unreliable (154) and the currently accepted practice for accurate diagnosis is upper GI endoscopy with subsequent histological confirmation.

Visually, Barrett's oesophagus appears as a velvety, dark salmon-pink mucosa extending proximally from the gastric folds. It contrasts sharply with normal squamous mucosa that lines the rest of the oesophagus, and appears as a pale, pinkish-white mucous lining the rest of the oesophagus.

The use of various dyes during endoscopy have been shown to offer some benefit in illuminating areas of possible Barrett's mucosa and are used by a number of upper GI endoscopists. Lugol's iodine (5mls of 50% solution) stains the squamous epithelium black and may aid in enhancing the contrast between this normal mucosa and the more distal CLO at the SCJ (155).

Areas of intestinal metaplasia have been shown to take up methylene blue (156), although ulcers may also take up this dye.

Magnification endoscopy is a relatively new technique and when used in conjunction with staining by 0.1% indigocarmine may enhance the ability to visualise areas of IM and even dysplasia (157).

Laser induced fluorescence spectroscopy has been used to detect areas of HGD (158), as has endoscopic ultrasound with varying results for both HGD and adenocarcinoma (159).

Histological diagnosis of CLO and cancer:

Dysplasia – cancer sequence

A sequence of progression from columnarisation, through metaplasia, to dysplasia and finally adenocarcinoma has been defined (see Figure 1), however histological recognition at each of these stages can be difficult and is also subject to varying degrees of inter-observer variation.

Diagnosis particularly of low-grade dysplasia can be inconsistent. (160).

Interobserver agreement in the diagnosis of HGD and intramucosal carcinoma as separate from LGD, indefinite for dysplasia and no dysplasia is in the region of

85%, and falls to 72% when distinguishing all grades of dysplasia from no dysplasia. In a recent study by Montgomery et al (161), intra and interobserver agreement were near perfect in distinguishing CLO/indefinite for dsysplasia and LGD from HGD and AC (kappa 0.82 (intra) and 0.66 (inter)) and substantial to moderate in separating CLO from indefinite dysplasia/LGD, HGD and AC (kappa; intra = 0.64, inter = 0.43). Overall, interobserver agreement was substantial for HGD/AC (0.65), moderate for CLO (0.58), fair for LGD (0.32) and slight for indefinite for dysplasia (0.15).

Other markers aside from the presence of dysplasia may be useful in managing and preventing the development of oesophageal adenocarcinoma.

Sulphomucin expression in the columnar-lined mucosa may be relevant to the development of malignancy, however it is often present in non-dysplastic CLO(162).

Molecular markers such as EGF, c-erbB2, TGF-alpha and p53 have all been investigated as potential predictors of adenocarcinoma (163).

Flow cytometry is another new technique involving measurement of cellular DNA content that has been evaluated as a potential way of predicting carcinogenic change with varying levels of success (164).

Biopsy techniques

In 1993, Levine et al (165) demonstrated that using a sampling technique where the oesophageal mucosa is biopsied from four quadrants at distances 2cm or less along the lesion using large channel biopsy instruments, then it is possible to accurately distinguish between high-grade dysplasia and early adenocarcinoma. Since this study, many of the guidelines produced on the management of CLO and dysplasia in CLO have recommended adopting a similar biopsy technique.

Guidelines for the diagnosis of CLO

In the 2002 British Society of Gastroenterology (BSG) guidelines for the management of gastric and oesophageal cancer (166) it is mentioned that '*..the diagnosis of Barrett's is based on a combination of visual appearance and*

standard biopsy specimens...'. but whether a histological confirmation of CLO + IM, or even of CLO alone is a prerequisite for a diagnosis of Barrett's is unclear. Short segment specialised columnar epithelium is defined as IM in a columnar-lined segment less than 3cm in length. The presence of IM in the gastric cardia has been referred to as 'ultrashort' segment Barrett's, although they mention that the malignant potential is probably lower than IM elsewhere and that this condition is 'more likely to be associated with H-Pylolri infection than GORD'. The length of Barrett's is defined precisely as '*...the distance between the transition from oesophageal mucosa to gastric mucosa (Z-line) and the upper end of the gastric folds, the position of the Z-line being recorded in cm from the incisors....*'(167). The practice of taking 4 quadrant biopsies at 2cm intervals (165) is mentioned as a method of detecting HGD and microscopic AC; and the use of jumbo forceps is suggested may improve sampling.

The 3 types of histological appearance of Barrett's suggested by Paull et al (69) - as mentioned previously – are quoted. It is suggested that Barrett's change can be present with or without IM, a view that has provoked some controversy and one that differs significantly from most gastroenterologists in the United States. Inconsistencies in the histological interpretation of dysplasia are highlighted, particularly when the process of regression has led to the presence of underlying regenerative inflammatory atypia, an appearance which may be mistaken for HGD. Finally, it is recommended that oesophageal biopsies be examined by 'an experienced histopathologist' and that the diagnosis of HGD be corroborated by a separate pathologist – '*a "lead pathologist" in gastrointestinal pathology...*'.

The American College of Gastroenterology (ACG) guidelines published in 1998 (168) are slightly different. They define Barrett's oesophagus as *'..a change in the esophageal epithelium of any length that can be recognised at endoscopy and is confirmed to have intestinal metaplasia by biopsy.'* It is immediately apparent that this differs from the U.K. definition of CLO where the presence of IM is not a prerequisite for diagnosis. The presence of IM at the cardia is distinguished from short segment CLO and is defined as a disease of the stomach with uncertain pathological implications. Emphasis is on precise recognition of the SCJ and OGJ

in order to make an accurate diagnosis. The incorporation of specific endoscopic staining techniques – including Lugol's iodine, toluidine blue, indigo carmine and methylene blue – are mentioned, although it is suggested that these have not been reproducibly demonstrated to improve recognition of the Barrett's segment. The actual numbers of biopsies needed for an accurate diagnosis of CLO is not clear but it is suggested that the more biopsies that are taken the greater the likelihood of recognising IM (169). The technique of taking 4 quadrant biopsies at 2 cm intervals is mentioned but not actively endorsed, and is mainly in the context of surveillance for the detection of dysplasia and adenocarcinoma. 4 quadrant biopsy technique every 1cm is mentioned in the updated guidelines 2002, and it is suggested that it may have an increased sensitivity for pick up of AC (170) but is suggested that it is likely to be difficult in the clinical setting due to the considerable increased workload it involves.

Sampliner et al recommend the use of alcian blue stain at pH 2.5 (171) for the recognition of Goblet cells; the hallmark of intestinal metaplasia.

In the updated guidelines published in 2002, Sampliner et al mention the use of new flow cytometric and loss of heterozygosity (LOH) techniques (172) in the prediction of patients at risk of the development of adenocarcinoma, and suggest that in combination with histology these techniques may prove useful in planning surveillance follow-up protocols for patients with CLO.

2005 UK guidelines

The most recent UK guidelines for the diagnosis of CLO were published in 2005 (18). Emphasis, firstly, is made on the ability to recognise the macroscopic diagnosis of CLO based on precise anatomical landmarks; definitions of which have been described in a publication by the European Society of Gastrointestinal Endoscopy (167). The length of CLO is defined as '*..the distance between the transition from oesophageal mucosa to the gastric mucosa (Z-line) and the upper end of the gastric folds, the position of the Z-line being denoted in centimetres from the incisors.*'

Histologically, 4 categories have been defined for reporting diagnostic biopies: 1) biopsies diagnostic for CLO, 2) biopsies corroborative of an endoscopic diagnosis of CLO, 3) biopsies in keeping with, but not specific for CLO and 4) biopsies without evidence of CLO. The first category is based on the histological recognition of native oesophageal structures in the presence of metaplastic glandular mucosa; whereas categories 2 and 3 rely on the precise site of endoscopic biopsy and may be misinterpreted if stomach or GOJ inadvertently biposied. Short segment CLO is defined by a histological diagnosis of intestinal metaplasia in the distal oesophagus in <3cm of recognisable columnarisation. The diagnosis of 'Ultra-short segment CLO', however, is essentially a histological diagnosis, where IM is detected in cadiac mucosa adjacent to a normally sited SCJ. More recently this has been described as cardiac intestinal metaplasia (CIM), the relevance of which is debatable. Although the term 'specialised intestinal meatplasia' has been coined to describe the rather characteristic features of IM in CLO, the authors of these guidelines stress that, in their opinion, there are no strictly pathognomonic histological features of CLO. In terms of biopsy technique, a number of points are derived from the Second European Endoscopic Forum (173). The first is that a specific biopsy protocol for optimal diagnosis has yet to be proven, secondly, jumbo forceps are not recommended for routine diagnosis, thirdly, there is no justifiaction for routinely biopsying an endoscopically normal SCJ and lastly that tongues of columnar epithelium should be biopsied.Contrary to current opinion in the USA, these UK guidelines still advocate that IM is not a prerequisite for the diagnosis of CLO.

Since publication of these guidelines outcome of a study stemming from a consortium held in Prague and published in 2006 has led to the development of the so-called 'Prague C and M criteria' (174). This is a validated system for assessment and documentation of the extent of macroscopic disease observed at endoscopy, with both circumferential disease (C) and non-confluent disease (M) recorded appropriately.

Helicobacter Pylori

Helicobacter pylori (*H pylori*) was first successfully isolated by Warrren and Marshall in 1983 (175). Its genomic sequence was published 14 years later in 1997 (176) demonstrating a relatively simple organism consisting of 1.7 million nucleotides (dependent upon the strain of the organism) and representing approximately 1600 genes; 45% of which are unique to *H pylori*.

Virulence

The ability of *H pylori* to induce pathological changes in the host is very dependent on the specific strain of organism. The nature of the pathological outcome, be it peptic ulcer, atrophic gastritis, intestinal metaplasia or gastric cancer is also largely determined by the gentotypic variance of the bacterium itself.

Strains of *H pylori* vary either in mutations of the nucleotides themselves, or in segments of DNA that have been transmitted by other bacteria and either incorporated into the DNA sequence of the host or that remain separate to the chromosome of the recipient as a plasmid. Some of these new DNA sequences will code for various virulence factors and are known as pathogenicity islands (PAIs) (177).

The virulence of *H pylori* seems to be related mainly to two genetic factors:

1. the segment that codes for the vacuolating toxin and
2. a pathogenicity island known as the cytotoxin associated PAI (cag PAI).

The cag PAI is a 40 kilobase segment of DNA that codes for around 40 proteins. It has a different proportion of bases than the rest of the helicobacter chromosome suggesting that its DNA has come from a foreign source and has features in common with *E.Coli, Yersinia pestis* and *vibrio cholera* suggesting it may have been derived originally form these organisms.

One of the 40 genes contained on the PAI is cagA (178) which codes for cytotoxin associated antigen. It is found in organisms that secrete the vacuolating

toxin (179) and induces a measurable antibody response in patients who become infected.

Cag A strains are more efficient inducers of epithelial cell NF-kB (180) than other strains.

The vacuolating toxin (discovered in 1988 (181) ref 1;10) causes vacuolation in cell cultures in vivo and damage to gastric epithelium in mice in vivo studies(182). It is coded for by the vacA gene which is not part of the PAI itself, but only appears to express the toxin when the PAI is present. The toxin is activated at low pH and is resistant to acid and pepsin.

H pylori tends to colonise the surface epithelium beneath the mucosal barrier where the pH approaches neutrality. It has been shown to cause accelerated cell desquamation and leads to a polymorph and chronic inflammatory cell response in the gastric mucosa. *H pylori* gastritis induces the release of prostaglandins, cytokines and nitric oxide which promotes an inflammatory response and mucosal damage (183) (184) (185).

The inflammatory pathway is thought to be mediated via the release of complement components liberated through the activation of the alternative pathway; and the release of proteases may be responsible for glandular destruction and the subsequent atrophy that characterizes the established disease.

In the acute phase of *H pylori* infection it tends to be the gastric antrum that is affected but in long-standing cases the entire stomach may become involved resulting in widespread glandular atrophy, fibrosis and intestinal metaplasia.

It is now largely accepted that the most common cause of chronic gastritis is *H pylori* infection.

Although predominantly affecting the stomach, duodenitis may result when patches of heterotopic gastric mucosa or gastric metaplasia exist and become infected (186).

There have been some studies that have suggested *H pylori* may colonise the oesophagus; (187) (188) (189) however, others have argued that this may simply be a reflection of contamination of gastric refluxate (190).

Sharma (190) and Henhihan (191) found that *H pylori* only adhered to *gastric* metaplasia in the oesophagus (not considered a premalignant condition) and never to areas of intestinal metaplasia.

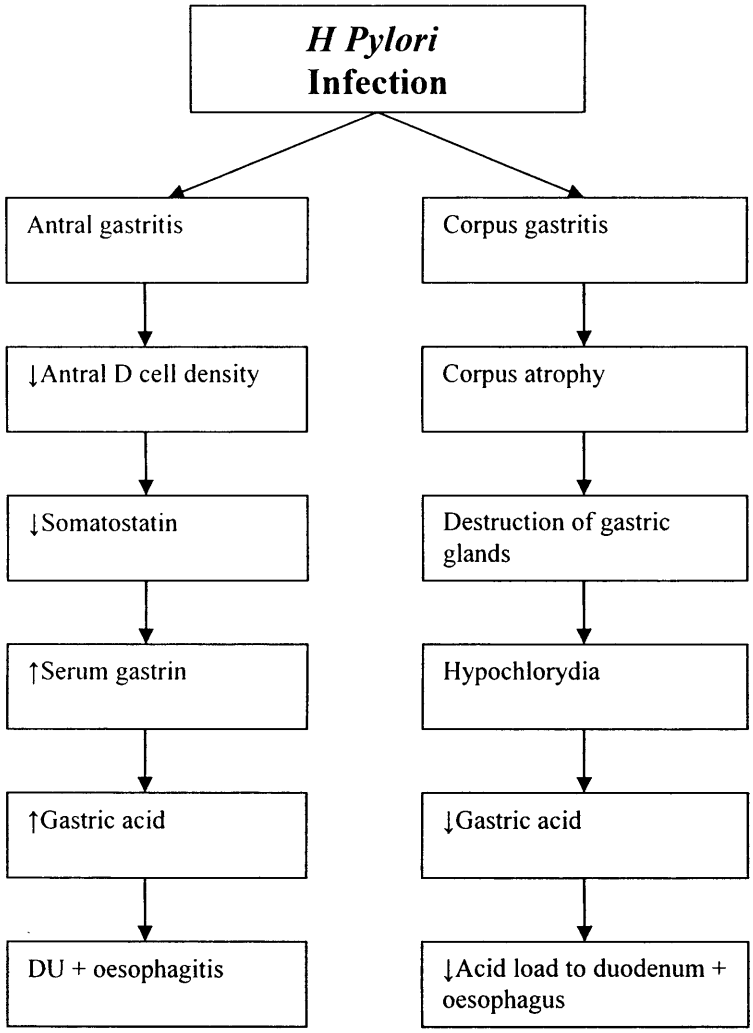
It has been postulated that the distribution of *H pylori* within the stomach itself and the subsequent pattern of gastritis, however, may result in significant differences in clinical outcome (see Figure 2). For example, *H pylori* affecting the gastric antrum and causing a predominant antral gastritis may then lead to a decrease in antral D cell (somatostatin producing) density (192) (193) (194) (refs 37-42; ref 4 Lee). This has been shown to lead to a decrease in the serum levels of somatostatin with a subsequent rise in the levels of gastrin (when the corpus of the stomach remains healthy) with the resultant effect of an increase in gastric acid production leading to duodenal inflammation or ulceration (DU) and GORD.

H pylori affecting the gastric corpus, however, (often cagA strains) can lead to a corpus gastritis (in chronic infection) which leads to a corpus atrophy (a known premalignant condition) with destruction of gastric glands. The resulting achlorydia may lead to decreased acid loads in the duodenum and oesophagus.

The theory that *H pylori* infection may have a *protective* affect on the development of oesophageal disease via this mechanism has been postulated by a number of authors. (195) (196) (197)

Figure 2

Patterns of gastritis and subsequent effects after *H pylori* infection



After eradication of *H pylori* it has been shown that the expression of H+/K+ ATPase pumps increases without an increase in parietal cell number (198) (199).

The aetiology and significance of inflammation at the GOJ/cardia region (carditis) is controversial. Goldblum et al (151) have shown a significant correlation with carditis and HP infection, and also that this is related to intestinal metaplasia at the cardia (a controversial finding not supported by Bowreys findings)– and not associated with GORD (so called *ultra-short segment Barrett's* by some physicians). Bowrey et al (200) found 2 distinct types of carditis – one that appeared to be associated with *H pylori* and one that wasn't and postulate that reflux may be involved in a proportion of cases, possibly sensitising the cardia mucosa to further injury.

Methods of detection of HP

There are many ways of testing for the presence of *H pylori* infection. A mucosal and systemic inflammatory response in the host allows *anti-H pylori* IgG antibodies to be detected in patient's serum, saliva, urine or stools. *H pylori's* ability to produce urease, an enzyme that catalyses the hydrolysis of urea to form carbon dioxide and ammonia, allows testing based on this reaction and is the basis behind the radiolabelled carbon-urea breath test and *campylobacter-like organism* (Clo) test.

The breath test, using either radioactively labelled carbon 13 or carbon 14, has been shown to be more accurate than serological tests and sensitivities have been quoted as much as 99% and 100% with 100% specificity (201). The stool antigen test has also been shown to be extremely accurate, as has the Clo test, both with sensitivities and specificities ≥ 98% (202).

After eradication therapy, the Breath test, Clo and stool antigen tests are all accurate methods of detecting *H pylori* status, however, serology is not as the antibody remains in the serum long after succcessful eradication.

Table 2 Methods and accuracy of *H pylori* detection

Test	Sensitivity (%)	Specificity (%)	Relative cost
Culture	77-92	100	High
Histologic study	93-99	95-99	High
Rapid urease test (Clo)	89-98	93-100	Low
Serologic test	88-99	86-100	Low
C13 breath	90-100	98-100	Moderate
C14 breath	90-97	89-100	Moderate

Summary of Table from Zeigler web site (202)

GORD/CLO and Adenocarcinoma

The association between *H pylori* infection and oesophageal disease is controversial, and observational studies have led to varying conclusions. Mechanisms of potential GORD due to the presence of *H pylori* have been proposed. Alterations in acid regulation as a result of an *H pylori*-induced gastritis have been described and have been discussed previously. Other proposed mechanisms include impairment of sphincter function via increased TLOSRs (203), impairment of gastric emptying (204), direct effects on oesopahgeal mucosa of *H pylori* induced (205), and increased LOS dysmotility (43).

Boyd observed that patients with DU were also more likely to suffer from reflux oesophagitis implying, perhaps, a common *H pylori*-induced patho-aetiology (206). Young et al (207) found dysplasia significantly more common in patients with *H pylori* infected Barrett's mucosa, when type 3 IM existed.

Sharma et al (208) reported a significantly higher prevalence of *H pylori* in patients with AC compared to those with SCC oesophagus.

Reports of the overall prevalence of *H pylori* infection in patients with CLO, varies in the literature (see table 3). Loffeld et al (209) found an overall prevalence of *H pylori* in oesophageal biopsy specimens of 62% in patients with CLO; and a higher prevalence in patients between the ages of 21 and 40 (80%) compared to patients in this age group with non-ulcer dyspepsia (38%) and healthy controls (24%). However, the difference in prevalence between the CLO group and the non-ulcer dyspepsia group got less as the patients got older.

Conversely, many studies have not shown a detrimental affect of *H pylori* on reflux-induced oesophageal disease.

Schenk et al (210) observed that *H pylori* negative patients had a more severe oesophagitis and more frequent CLO at baseline endoscopy than those that were *H pylori* positive.

Rugge (211) found a significantly lower prevalence of *H pylori* infection in patients with CLO compared with controls and also noted that the histological severity of non-atrophic gastritis in the controls was significantly higher than that detected in patients with CLO.

On serology, Grimley et al (212) found significantly higher frequency of *H pylori* antibodies (Cag A and Vac A) in patients with DU and gastric carcinoma when compared to oesophageal adenocarcinoma and controls – and a higher prevalence of *H pylori* antibodies in the control group when compared to the AC group (although this did not reach significance; 17% vs 10%).

In a study of 343 patients (114 with AC) Oberg et al (213) did not find any significant differences in prevalence of *H pylori* infection and severity of oesophageal disease and conclude by saying that *H pylori* plays no role in the pathogenesis of GORD and its complications. Their prevalence of *H pylori* infection (on gastric antral biopsy) in benign, symptomatic disease was 14% compared with 19% in patients with AC.

Labenz (214) demonstrated a significant increase in development of reflux oesophagitis in patients with DU having had their *H pylori* eradicated when compared to patients who did not undergo this treatment and was one of the first to put forward the hypothesis that *H pylori* may provide a protective role in preventing the development of reflux-induced oesophageal disease (215) (216) (217). A decreased risk of oesophageal and gastric cardia adenocarcinoma in patients who were *H pylori* positive has also been demonstrated by a number of authors (218) (219) (220).

O'Connor et al (221) did not demonstrate any association between *H pylori* infection, severity of oesophageal inflammation or length of CLO.

Table 3 Prevalence of HP infection in controls and reflux-induced disease in various studies

Author (date)	Controls	DU	GORD	Oesophagitis	CLO	AC
Loffeld (1992)	-	-	-	-	62%	-
Newton (1997)	36%	94%	-	36%	25%	-
Hacklesberger (1998)	-	89%	-	38.5%	-	-
Henihan (1998)	-	-	0%	-	23%	0%
Grimley (1999)	17%	48%	-	-	-	10%
Oberg (1999)	-	-	14%	12%	13%	19%
Rugge (2001)	-	-	57%	-	36%	-

In 1900, gastric cancer was the leading cause of cancer death in the USA and Europe. The dramatic fall in non-cardia gastric adenocarcinoma since then has been explained at least partly due to the fall in *H Pylori* infection. Over the same time frame, however, the coinciding increasing incidence of oesophageal adenocarcinoma and gastric cardia cancers is less easy to explain.

Adenocarcinoma of the oesophagus and cancer of the gastric cardia are anatomically and nosologically similar, and it does not seem surprising that their incidences should rise at the same time.

Certainly there has been a documented increase in the rates of GORD since the 1930s, and since the first scientific classification of a presumed pre-malignant oesophageal histological condition by Barrett in 1950, rates of CLO have increased dramatically.

Even more recently, there have been marked epidemiological changes in upper gastro-intestinal disease patterns observed throughout the western world (222). Hospitalisation and mortality rates for DU, gastric ulcer and non-cardia gastric cancer – all *H pylori* related diseases – have declined markedly between 1970 and the present in Europe and the United States. However, in conjunction with these

observations, both hospitalisation rates and mortality for GORD and AC in these areas have increased dramatically over the same period.

These findings provide the epidemiological basis for an association between *H pylori*, GORD and AC; but physiologically it is less easy to demonstrate a direct relationship.

Once acquired, *H pylori* infection has been shown to persist throughout the life of the host.

Blaser (223) argues that there is evidence to suggest that *H pylori* has been part of the 'normal' microbiota of humans for millions – if not tens of millions - of years, and that a form of 'co-evolution' will have arisen over this period of time. He suggests that it is likely that an intricate symbiotic relationship has evolved and that certain physiological functions taken for granted – eg. regulation of gastric acid output – depend on this relationship.

The widespread eradication of the organism may have a substantial effect on the physiological mechanism of acid production.

Geographically, patterns of *H pylori* infection and *H pylori* related disease varies. The specific strain of *H pylori* also shows geographical variation.

H pylori are highly polymorphic, and multiple strains may colonise the same host at the same time (224) (225) (226). Cag A +ve and –ve strains may also exist in the same host.

In Latin America, Western Europe and the Unites States only 40 –60% of carriers are cag A +ve, whereas in East Asia, most are Cag A +ve (227) (228).

The pathogenecity of the organism also seems to differ in these regions with the significant association of DU, atrophic gastritis and non-cardia gastric cancer seen in the USA, Europe and Latin America; but not observed in many Asian populations.

GORD is uncommon in countries where most adults are *H pylori* positive (especially Cag A) (229) and recent studies have shown that the prevalence of *H pylori* is lower in people with GORD when compared to controls (215) (216) (217).

There is a lot of evidence to suggest that over the course of industrialisation the incidence and prevalence of *H pylori* has been progressively declining (230) (231) (232).

Early childhood crowding is a risk factor for *H pylori* acquisition (233) and recent studies suggest that higher birth order and older siblings within 5 years are at the highest risk of becoming infected (234). Blaser (178) points out that there is evidence to suggest that children are the major 'amplifiers' of *H pylori* in the population and thus the trend towards lower birth rates and smaller household size seen over the last 100 years or so may be a significant factor in the drop in *H pylori* infection rates. The widespread use of antibiotics for many different illnesses has also coincided with this drop and is no doubt a major factor.

Although it has been shown that a single regimen antibiotic course is only perhaps 5-10% effective in eradicating *H pylori* (235) (236) (237) this level of eradication may have significant effects at a population level.

Interestingly, peptic ulcer disease (PUD) was a relatively 'new disease' at the beginning of the 19th century in Europe and the USA and its incidence was rising at a time when *H pylori* infection was already beginning to decline.

Whether it is the change in population strain of *H pylori* or maybe the age of acquisition that are the important epidemiological factors in its pathogenesis is not clear. Blaser suggets that it is the specific microenvironment of the stomach and changes related to this that are important in understanding changing patterns of disease.

Treatment of H pylori

The treatment of *H pylori* and GORD has also been shown to alter the distribution of the organism throughout the stomach with a corresponding change in pattern of gastritis and clinical result (238).

Long term proton pump inhibitor treatment has been shown to alter the distribution of H pylori in the stomach from an antral to a corpus or fundus prevalent pattern. This may enhance progression of *atrophic* gastritis, a well-documented risk factor for the development of gastric cancer. This is the basis

behind the argument that patients who require long-term proton pump inhibitor therapy should have their *H pylori* eradicated. It is particularly relevant to patients who suffer from GORD and may have either oesophagitis or CLO, as they undoubtedly require long-term therapy of this nature.

In 1996, Kuipers et al published a study suggesting that omeprazole accelerated the development of corpus atrophic gastritis in *H Pylori* infected subjects (239). However, a number of authors have since published findings that do not support this hypothesis (240) (241) (242). A consistent finding, however, amongst many authors has been the change in pattern of gastritis observed from an antral predominant to a corpus predominant distribution in *H pylori* infected patients on long-term proton pump inhibitor therapy.

Recent studies (243) have postulated that a corpus gastritis alone may well have significant malignant potential – without the need for the presence of gastric atrophy.

Although many studies recently have reported low rates of *H pylori* infection in patients with both oesophagitis and CLO, and derived from this the theory that *H pylori* infection may indeed offer some 'protection' to the development of oesophageal disease (195) (244), this is still a fairly contentious issue.

In a recent study by Kuipers et al (245), they found a significant reduction in gastritis after *H pylori* eradication therapy with no significant increase of symptoms of GORD or presence of endoscopic erosive oesophagitis, and conclude by continuing to recommend eradication of *H pylori* in patients on long term proton pump inhibitor treatment.

Surveillance of patients with CLO

Reported overall survival in patients diagnosed with oesophageal adenocarcinoma has varied over the years but remains fairly poor.

For unresectable oesophageal tumours the 5 year survival rate has been estimated as low as 1% (246) (247). After complete/attempted curative resection, overall 5 year survival rates have been reported by some as being up to almost 60% (248). Menke Pluymers et al. (249) showed a five year survival rate of 24% but demonstrated that this improved to 30% if no involved regional lymph nodes were found at resection, and 63% if the tumour was confined to the submucosa. Interestingly, they found that histological grade of tumour did not seem to influence survival outcome.

DeMeester et al (250) report a five year survival of 53% for what they call a 'curative' resection, involving en-bloc dissection of the distal oesophagus including proximal stomach, spleen and splenic artery, and a fairly radical lymph node resection. They were, however, fairly selective with their patients with preoperative criteria only including patients with a tumour size of <5cm (and involving less than half of the oesophageal circumference), no associated lymph node involvement on CT and under the age of 75 classified as 'physiologically fit'.

DeMeester found that in patients with intramucosal AC, none had metastasized to regional lymph nodes, and therefore recommend simple oesophagectomy in this group of patients. In intramucosal and transmucosal disease they conclude by suggesting en-bloc dissection with splenic preservation.

In a cohort consisting of a high number of stage 0 and 1 adenocarcinomas, Lerut et al (248) demonstrated a 58.2 % overall five year survival rate. When broken down per stage of disease, survival varied from 0% for stage 4, right through to 100% for stage 1. They also found a statistically better 5-year survival in patients who underwent radical resections with extensive lymphadenectomies than in those treated by simple resection

These studies seem to highlight the finding that early diagnosis of AC has a significant impact, not only on survival figures, but on the type of operation that the patient undergoes.

The five year survival rate form 'curative' resection has improved dramatically over the last 20-30 years from approximately 14% to 60%, with recent more radical resections contributing significantly to this finding (251).

There is, however, significant mortality and morbidity associated with oesophageal resection itself. On a worldwide review of mortality following oesophagectomy for all types of oesophageal cancer, Jamieson et al. (252) found a mortality rate of 6.4% post operatively for adenocarcinoma.

However, this is a significant improvement compared with results from 30-40 years ago. From 1960-1979 the overall 30 day post-operative mortality rate for all types of oesophageal cancer was reported as 29%, from 1980-1988 the rate was 13% and in this recent review a rate of 6.7% for the period between 1990-2000 was demonstrated.

There is a possibility, however, as Jamiesion et al point out, that various factors may confound these figure. For example, the improvement in post-operative and intensive care may make 30 day figures look good but survival after this period may still be fairly poor; and careful patient pre-operative selection criteria may also bias the figures towards an apparent improved survival rate.

The impact of regular surveillance for patients with CLO in an attempt to detect AC at an earlier, more treatable stage, is controversial.

In a comparative study of stage of disease found post oesophagectomy in patients under surveillance for CLO and those picked up symptomatically, Van Sandick et al (253) found a significant higher number of earlier stage disease in the surveyed group. They reported two-year survival rates of 85.9% in the surveyed patients versus 43.3% in the non-surveyed group.

They found no difference in the histological grade of tumour between the groups.

Peters et al (254) reported an 85% five year survival compared with a 20% survival in surveyed versus non-surveyed patients respectively.

Fountalakis et al (255) found a significantly earlier stage of disease in patients undergoing surveillance compared with those presenting symptomatically, with a subsequent impact on survival rates.

In a Markov computer model, Provenzale et al (256) constructed a cohort simulation of 10,000, hypothetical 55 year old men with CLO. To put things into perspective they compared total life expectancies for patients this age and estimated the average life expectancy of a 55 year old man to be 24.5 years. For patients with CLO who do not undergo surveillance, they calculated the life expectancy to be approximately 4 years shorter (20.6 years), and for patients undergoing surveillance with oesophagectomy for cancer life expectancy was increased over the non-surveillance group by 1-1.4 years (21.6-22 years); with an extra 1-1.2 years added if oesophagectomy for HGD was included. However, interestingly, when quality adjusted life expectancy was incorporated, these additional years dropped to 0.4-0.7 and 0.5-0.6 years respectively.

They estimated that 27% of patients with CLO who do not undergo surveillance would develop cancer over their lifetime. The shortest surveillance intervals resulted in the greatest reduction in cancer incidence and this incidence was lowered even more when oesophagectomies were carried out for HGD (a 74-89% reduction compared to no surveillance); presumably due to the fact that there were less patients left to develop AC in this strategy.

Lerut et al (248)found that in patients undergoing surveillance, an 'early' diagnosis was made in 82% of patients (73% of them had no lymph node invasion), although they made the important observation that only a small number of the entire cohort (less than a third) of patients had been enrolled in a surveillance programme prior to their diagnosis.

There have been a number of studies in the U.K. over the last few years looking at the impact of surveillance programmes on the diagnosis and outcome of Barrett's adenocarcinoma.

MacDonald et al (134) presented their results of a screening programme for patients with Barrett's spanning a ten year period from 1984-1994. 143 out of 409 patients with CLO were entered into the programme (35%); patients over the age

of 70 years or with significant comorbidity being excluded. The average surveillance period per patient was 4.4 years. 20% (n=33) of patients died during the surveillance period; 3 from AC and 30 form other causes. However, only one of the adenocarcinomas was detected on 'routine' screening.

During the same 10 year period the unit detected 466 patients with carcinoma of the oesophagus (SCC and AC) on initial diagnostic biopsy (ie prevalent cancers) – 10 of whom were proven AC in Barrett's metaplasia.

In the non-surveyed patients, 1 died of AC (too frail to be entered into a screening programme) and 103 died of other causes.

They were understandably unimpressed by the benefits of maintaining such a programme and concluded by saying that the added workload incurred by having the programme (379 screening endoscopies) amounted to the equivalent of one months work by the entire endoscopy unit. They suggested that screening be more targeted towards possibly longer segment disease (>8cm) or towards patients with associated oesophageal strictures or ulceration.

The practice of surveillance throughout the U.K., although increased in general over the last 10 years or so, is still understandably inconsistent; with differing surveillance intervals employed for various grades of histological disease and precise techniques utilised for oesophageal endoscopy and biopsy varying from centre to centre.

Smith et al (257) received 152 replies from questionnaires sent in 1997 to randomly selected members of the British Society of Gastroenterology. At that time 70% admitted to surveying regularly for CLO. 46% of them had a selective policy for enrolment into surveillance programmes determined by length of CLO segment, presence or absence of dysplasia or age. 55% surveyed at 1 yearly intervals, 26% 2 yearly, and the rest varied. Surveillance for LGD varied from 6 monthly to yearly to direct referral for surgery (for one patient).

67% took a set number of biopsies regardless of length of CLO segment and 8% took 4 quadrant biopsies every 2 cm. For 'severe' dysplasia the majority of endoscopists recommended referral for surgery.

Mandal et al (258) obtained data via a questionnaire in 2001 involving 203 gastroenterologists. 76% of them, at that time, performed surveillance for CLO. 80% of those that surveyed said that they used some sort of 'selection criteria' - including age, length of segment, presence of ulcers or strictures - to enrol their patients.

62% did not survey for Barrett's segments <3 cm. 77% followed some sort of protocol, with 46% admitting to using a '4 quadrant biopsy' technique for obtaining biopsies. The surveillance interval for uncomplicated CLO varied, although almost half employed a 2 yearly interval.

For patients with a diagnosis of HGD, 74% repeated the OGD within 6 months with 23% making a direct referral for surgery. 70% asked for 2 experienced pathologists to review the results.

Although Levine (165) argues that a rigorous *'4 quadrant biopsy technique'* is able to distinguish accurately the presence of HGD, intramucosal and submucosal AC, the practice of this protocol in the U.K. for patients undergoing surveillance for their CLO seems fairly limited. There is no doubt that the extra workload enforced upon the pathologists alone by sending this vast number of biopsy specimens (up to 20 sections in a 10cm length of CLO, for example) is a major consideration in an already overworked and under-resourced system.

Workload considerations aside, the overall costs for regular endoscopic surveillance is fairly substantial, and justification for the distribution of resources into this area is not an easy task.

In the USA, Achkar et al (259) estimated the cost of yearly endoscopic surveillance to be approximately $62,000; which worked out at $31, 000 per cancer diagnosed – more than 10 times the equivalent cost of haemoccult screening for colorectal cancer ($2,667 per cancer detected).

In the U.K. Wright et al (260) estimated the cost to detect one cancer whilst on a surveillance programme to be between £13, 860 and £28, 224 (approximately £15,000 for men and £42,000 for women). Gross et al (261) estimated an annual national expenditure in the USA of $23.1 million for a surveillance programme consisting of biennial endoscopies incorporating a 4 quadrant biopsy technique.

Interestingly, this reduced significantly to $15.4 million if the patient was followed up every 3 years. They also examined various 'non-clinical factors' that might affect individual physician's practices and found that a primary fee for reimbursement system had the most significant impact (OR 2.57, p = 0.004) on whether patients with uncomplicated CLO (ie. no dysplasia) were enrolled onto surveillance programmes.

Table 4 Variations in surveillance practice (UK and USA)

Author (ref)	**Endoscopists undertaking surveillance**	**Surveillance Interval (months)**		**Four quadrant biopsy technique**	**HGD management**
	Proportion	*CLO*	*LGD*	*Proportion*	*Surveillance/Surg*
Smith 1997(256)	70%	81% 12-24m	1-12m	8%	31% - surgery
Mandal 2001(257)	76%	46% 24m	-	46%	23% - surgery 74% - repeat OGD 6m
Gross 1999(260)	96%	59% 7-12 m	30% ≤ 3 m 60% 4-6 m	53%	73% - surgery 27% - surveyed 3-6 m

Recommendations for management of CLO

The American Cancer Society has outlined the prerequisites for an effective screening programme, which has been agreed should apply to oesophageal cancer (both squamous and adenocarcinoma) (262). The five main points that are highlighted are as follows;

'1. there should be convincing evidence that the procedure (screening procedure) is effective in reducing cancer morbidity or mortality;

2. there should exist individuals at increased risk from the diseases;

3. the screening procedure should be practical and feasible;

4. the costs of screening should be reasonable;

5. *the yield of the screening test must result in earlier diagnosis of the disease with a subsequent better survival of the identified patients (ie. the benefits of the screening should outweigh the risks).'*

Other considerations that apply to an effective screening programme include 'quality of life issues', such as disease related morbidity with and without treatment, and associated risks and morbidity associated with the screening procedure itself.

These points are similar to other screening and surveillance guidelines although many of them are left fairly open to interpretation.

The important points, however, include the recognition of the natural history of the disease, with an identifiable cancer precursor stage at which early intervention has been proven to have a beneficial effect on patient survival; and the employment of a screening procedure that is both acceptable to the patient and reasonably cost effective: both of which many would argue are largely unproven in Barrett's adenocarcinoma.

Many debates over whether to survey or not have often focussed on the benefit to the population as a whole, and the impact that early diagnosis and treatment can make on the overall mortality and morbidity figures associated with the disease. It is debatable whether screening for oesophageal adenocarcinoma fulfils this criterion either, as the evidence suggests there are still a vast number of patients in the population with undiagnosed CLO who will never be entered on to surveillance programmes and who make up the majority of prevalent cases of AC. However, there seems no doubt that the incidence of AC is increasing dramatically, and there is still a reasonably large body of evidence that supports the fact that early diagnosis can have a positive impact on survival; many authorities believe, therefore, in the implementation of surveillance for patients with CLO, and guidelines have been published.

A combination largely of the results of a working party discussion from the 1990 World Congress of Gastroenterology (263) and a study by Levine in 1993 (165), led to a number of recommendations for surveillance at the time, and became the basis for the publication of more formal guidelines a few years later.

At the time it was recommended that if the patient was fit for a potential oesophagectomy then they should enter into a regular endoscopic surveillance programme, involving 4 quadrant biopsies, preferably large-bore forceps, taken every 2 cm from immediately below to immediately above the area of columnarisation and that this should be assessed by a histopathologist with a particular expertise in this area.

If no dysplasia was found then biennial endoscopy was recommended.

If LGD was present then it was suggested that the patient be treated with a proton pump inhibitor for at least 3 months with repeat endoscopy after this time and then reversion to biennial endoscopy if regression of the dysplasia evident or continued 6 monthly surveillance if it persists.

For HGD, surgery or 3 monthly endoscopies with multiple biopsies was recommended.

In the UK published 'Guidelines for the management of oesophageal and gastric cancer' (166) recommendations for the diagnosis of Barrett's are mentioned, however, there is no specific endorsement for enrolment of patients into surveillance programmes, despite the fact that it is mentioned that cancers arising in areas of Barrett's detected by surveillance are often early and have a good prognosis. It is pointed out that the topic of surveillance is controversial and that eventually more targeted surveillance programmes may be more satisfactory.

It is recommended that a diagnosis of High Grade Dysplasia should warrant urgent endoscopic and histological review and that careful consideration should be given to resection. These such diagnoses should be confirmed pathological by a separate histo-pathologist – '..a lead pathologist in GI pathology..'

Sampliner et al (168) produced some guidelines for the management of CLO in 1998 with an updated version published 4 years later (264).

These recommend, firstly, that patients with long standing GOR symptoms, particularly those ≥ 50 years of age, should have upper endoscopy to detect possible Barrett's oesophagus. They suggest that all patients with CLO should undergo surveillance and that endoscopic intervals should largerly be determined by the presence and grade of dysplasia, although observation of an abnormal epithelial surface, such as a nodule or ulcer, requires special attention. For uncomplicated CLO (no dysplasia or abnormal mucosa) on 2 consecutive OGDs (with biopsy) a 3 yearly interval is deemed to be appropriate. For LGD they recommend annual endoscopy and for HGD they recommend 'intensive biopsy protocols', ideally with a therapeutic endoscope and large capacity biopsy forceps, requiring a repeat biopsy and confirmation by an 'expert pathologist'. For a subsequent diagnosis of 'focal HGD' (less than 5 crypts) they suggest 3 monthly surveillance and for 'multi-focal HGD' they recommend strongly considering 'intervention'.

The 1998 guidelines mention taking 4 quadrant biopsies at 2 cm intervals as previously described by Levine et al (165), but add in the updated version that this may not always be practical in the clinical setting.

There is controversy as to the exact management of HGD in Barrett's oesophagus. There is fairly substantial evidence that suggests that patients with HGD are at a significantly high risk of developing AC; some studies suggest up to 59% (75), and that AC may already exist in up to 40% of patients with HGD (128) (265) (266) (267). However, other studies have disputed this finding and suggested that surveillance for HGD with a careful biopsy protocol is a reasonable and safe strategy (74).

BSG 2005 guidelines (18)

With the advent of endoscopic modalities of treatment for dysplasia and AC, it has been argued that 'fitness for oesophagectomy' should not necessarily still be a requirement for entry onto a surveillance programme. The most recent BSG guidelines do not strongly advocate surveillance of all patients with CLO, however, but suggest it should be made available after an informative discussion

with the patient regarding the known pros and cons of this practice. In patients who undergo surveillance, endoscopy for non-dysplastic disease has been recommended every 2 years, with quadrantic biopsies every 2cm in the columnar segment together with additional biopsies of any visible lesion. If dysplasia is detected, then the guidelines recommend early re-evaluation with extensive biopsies after treatment with a PPI (for 8-12 weeks), and then 6 monthly endoscopy, until dysplasia is no longer detected. If HGD is detected and persists after intensive acid suppression with confirmation by two expert pathologists, then oesophageactomy is recommended in surgically fit patients. Those unfit for surgery should be considered for endoscopic ablation or mucosal resection.

Summary and overview of aims

The increasing incidence of CLO and its progression to AC is worrying. Risk factors for development of the disease, methods for making an accurate diagnosis and initiation of management plans have all been suggested; but there remains controversy in all of these areas.

This study sought to examine CLO and its progression to AC in a large cohort of patients registered with a national UK database. The UK National Barrett's Oesophagus Registry (UKBOR) was set up in order to answer some of these questions. Previous researchers based at the Registry have studied the natural history of the disease and the particular remit of this study was to examine patient characteristics and risk factors for progression of CLO, diagnosis of non-dysplastic and dysplastic disease, and the practice of endoscopic and histological surveillance. A largely epidemiological-based study, it was hoped that in examination of these areas we might, firstly, yield some information into the identification of patients at risk of developing cancer, secondly, gain some insight into techniques and consistency in diagnosing both pre-dysplastic and dysplastic disease and thirdly, be able to offer some evidence for optimising management of the whole spectrum of disorders from uncomplicated gastro-oesophageal reflux disease, through Barrett's CLO to adenocarcinoma of the oesophagus.

The main methods of this study involved collection and analysis of data on a large cohort of patients registered with UKBOR. For the remits of diagnostic and surveillance practice, data were also examined from responses to a questionnaire sent to gastroenterologists throughout the U.K.

A large part of the examination of patient characteristics and risk factors involved work on the impact of *Helicobacter pylori* infection on reflux-induced oesophageal disease; being a topical and somewhat controversial subject around the time of the study, and a separate chapter is dedicated to this.

The history and organisation of the UK National Barrett's Oesophagus Registry along with methods of data collection and workings of the database is described in the following chapter.

Patients and methods have been divided into statistical methods and analysis, 'General' – with many of the broad definitions and techniques used for a number of the above areas - and 'Specific', with details for analyses pertaining to specific topics explained in more depth.

Results for all of the analyses are grouped together, under separate topic headings, with a similar format used for the discussion.

The UK National Barrett's Oesophagus Registry (UKBOR) and study design

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UKBOR

History of UKBOR

The UK National Barrett's Oesophagus Registry (UKBOR) was set up in June 1996 as a joint initiative between the European Cancer Prevention Organisation (ECP) and the Oesophageal Section of the British Society of Gastroenterology (BSG). Initial discussions had begun the previous year between Dr Peter Reed (Consultant Gastroenterologist), Dr Christine Caygill (Clinical Epidemiologist/Biochemist), Dr Michael Hill (Consultant Gastroenterologist and Chairman of the European Cancer Prevention Organisation, ECP) and Professor Anthony Watson (Consultant Surgeon and Chairman of the Oesophageal Section of the British Society of Gastroenterology, BSG.)

The setting up of the registry was announced in Gut and in the European Journal of cancer Prevention (ECP) (268).

A Scientific Advisory Committee was set up in tandem with the registry and comprised of all the involved disciplines (endoscopists, surgeons, histopathologists, epidemiologists and statisticians). This currently meets annually to discuss gathered data to date, strategy, and registry priorities.

Currently the registry is overseen by 2 co-directors, Professor Marc Winslet and Dr Rebecca Fitzgerald - previously by Professor Anthony Watson – and is run by the registrar – Dr Christine Caygill. There are 2 post-graduate research fellows.

Registry aims:

The aims set out in 1996 were as follows: to establish a national database of all diagnosed cases of Barrett's Oesophagus in the United Kingdom, in order to provide information on:

1. prevalence of diagnosed cases, regional variations and variations with time
2. natural history and influence of medical, endoscopic and surgical treatment
3. incidence of oesophageal adenocarcinoma (AC) in Barrett's
4. rate of progression of CLO to AC
5. factors influencing rate of progression of CLO to AC

6. to provide a central resource for histopathogical confirmation of high-grade dysplasia, for molecular genetic studies and for all publications on CLO, which may be accessed by BSG and ECP members
7. to provide a co-ordination infrastructure for prospective studies of CLO, especially with the aim of reducing the risk of AC.

Funding

An initial sum of money to enable the registry to be set up was donated by a charitable trust as a result of efforts by Dr Peter Reed (Hon. Director). Since then the registry has largely been supported by the British Oesophageal Foundation (BOF), with the Wexham Institute of Gastroenterology (WIGIT) providing 2 years of funding for a research fellow.
Other financial support has been given by The Childwick Trust, The R L St. Harmsworth Memorial Research Fund and The David and Frederick Barclay Foundation.

Ethics

The collection and use of data is approved by the London Multi-Regional Research Ethics Committee (MREC).

Collection of data

Patients are currently registered from 44 registering centres spread throughout the U.K.(see Table 5/Figure 3) and covering an estimated catchment population of almost 11 million.
These centres all have a lead endoscopist with an interest in Barrett's Oeosphagus and volunteer to register patients diagnosed with CLO on a regular basis. Registration involves completion of a form (known as 'Form 1': see Appendix 1) which includes basic patient details such as name, date of birth and gender, as well as details of diagnosis of CLO – date, basic biopsy details, name of consultant. Since October 2003 informed consent has been sought to register patients.

These forms are sent to the registry and the 'registration' details are then entered onto the database (see general information table) at which time the patient is allocated a specific 'UKBOR' number. Once a reasonable number of patients are registered from a particular centre, then the patient's medical records are requested at that centre and these notes are examined on site. Relevant information is transferred onto another form – known as a 'Form 2' (see Appendix 2) and copies of endoscopy and histology reports made at the time. This form is then filed (as a hard copy) along with the relevant endoscopy and histology reports at the registry.

Inputting of data

Information from form 2s - and endoscopy and histology reports, which are regularly updated - are then entered onto the various tables on the database (see Appendix 3).

Figure 3 Distribution of centres registering with UKBOR throughout the U.K.

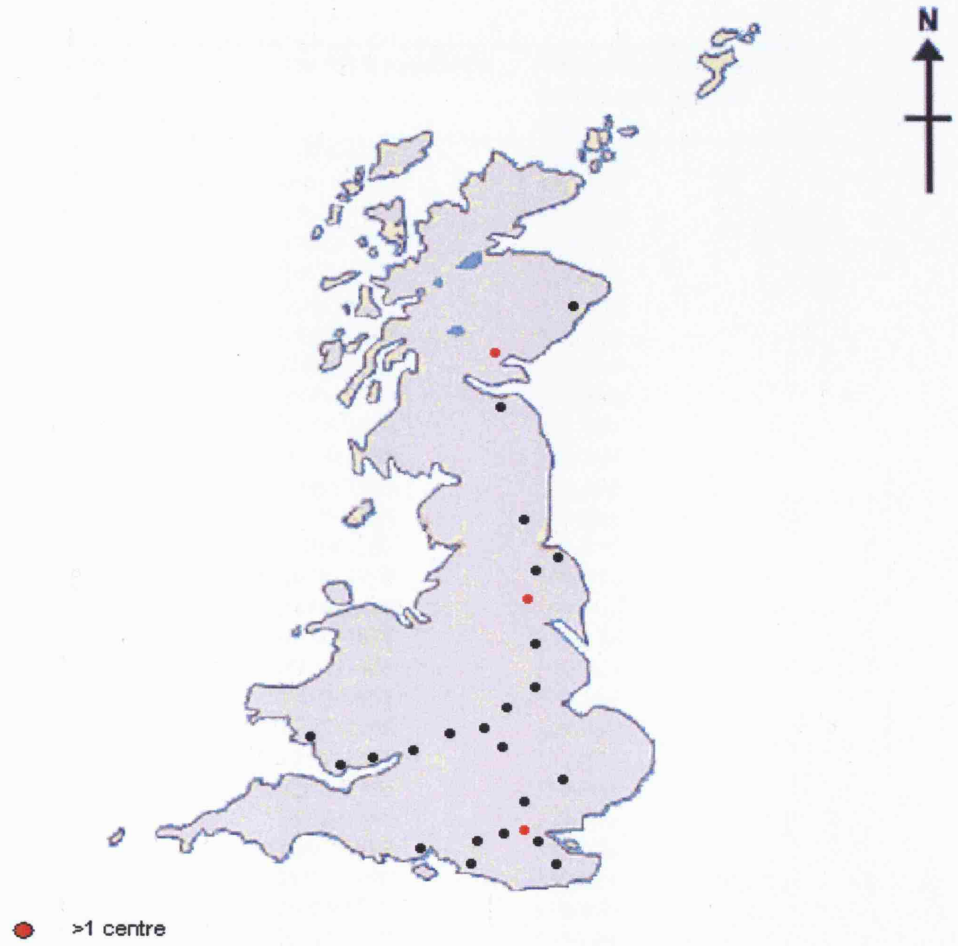


Table 5 Registering UKBOR centres; including number of patients registered to date and estimated catchment population size

Centre	Number registered	Date first registered	Catchment population Estimate (to nearest 500)
1	478	27/04/1999	330,000
2	259	09/12/1997	145,000
3	362	19/09/1997	250,000
4	3	17/04/1998	23,000
5	13	23/11/1998	315,000
6	8	01/07/2003	550,000
7	10	30/04/1998	250,000
8	602	20/06/2002	132,000
9	169	13/04/1999	250,000
10	9	21/05/1999	106,500
11	104	20/10/1998	250,000
12	316	24/08/1998	350,000
13	79	26/07/2001	150,000
14	52	12/04/2002	200,000
15	108	20/06/1998	300,000
16	48	21/06/1998	320,000
17	202	07/02/2000	250,000
18	121	09/11/1999	(see 43)
19	73	10/03/1997	500,000
20	79	12/12/1996	280,000
21	8	10/12/1998	37,500
22	421	02/12/1996	350,000
23	132	16/10/1998	209,000
24	13	14/07/1997	380,000
25	176	19/11/1996	380,000
26	12	26/04/1999	120,000
27	528	29/03/1999	137,000
28	787	09/10/1997	450,000
29	72	21/08/1998	300,000
30	23	01/04/1996	(see 43)
31	119	14/03/2002	300,000
32	142	07/05/1999	220,000
33	781	16/12/1997	200,000
34	103	22/07/1999	500,000
35	650	28/10/1998	254,000
36	117	28/10/1998	235,500
37	133	01/05/2000	320,000
38	128	17/05/2002	342,000
39	226	09/12/1997	100,000
40	77	17/10/1997	223,000
41	25	18/05/1999	250,000
42	557	23/07/1997	312,000
43	1319	11/04/1996	360,000
44	89	15/03/1998	300,000
Total	11,060		10,810,000

Design of the database

(in collaboration with Mr Piers Gatenby, Research Fellow)

The database was designed on a Microsoft Access programme (269) over a 3 month period from August-September 2004. The structure is a 'multi-platform' model with 8 separate but linked tables.

Basic demographic data are entered into a main 'parent' table labeled 'General Information' and consist of data with only one value (eg date of birth, gender, clinical outcome). Other clinical data are entered onto separate 'daughter' tables linked by a unique 'key' – a code number assigned to each patient – to the parent table. Daughter tables were able to contain multiple records for each patient (see Appendix 3).

Data are inputted into the tables under subheadings either in the form of a tick box format, or as freehand (See Appendix 3).

For the analyses, data were then either subtracted from the database using an access 'query' program, or transferred to an excel database. Information was then inputted into an SPSS statistics package (270) where all analyses were undertaken.

At the time of analysis 10,527 patients had been registered with UKBOR. Of these 1282 (12.2%) had been fully databased. The distribution of registered patients is shown in table 5.

The distribution of fully databased patients is shown below in Table 6:

Table 6 Fully databased patients per centre

Centre	Centre number for analyses	Number of patients
2	1	258
19	2	73
22	3	134
25	4	131
35	5	475
43	6	211
total		1282

Patients and Methods

.....

Statistical methods/analysis

Study design/analysis

This was a retrospective observational cohort study. Patients were divided into various groups retrospectively and analysed for varying independent variables; ie. as a *case control* study. Dependent and independent variables were defined separately for each analysis.

The dependent variable was 'dysplasia' or 'adenocarcinoma' for the majority of analyses (ie discrete variable); however, continuous metric variables such as 'survival time' and 'surveillance interval' were used for a number of studies. Descriptive and inferred data were explored and analysed by a number of statistical methods as described below.

Power

For all analyses p values <0.05 were taken as being significant (ie significance level = 0.05). In other words the probability of committing a type 1 error (α) was 5/100 (ie rejecting the null hypothesis when it is true).

Power was set at 0.80 (the level of committing a type 2 error (β) was 0.2); ie. we were confident that with the majority of our sample sizes we could detect a 20% difference in response rate between the cases and the controls (see Table 7). Sample sizes were adequate for 2-tailed testing for the vast majority of analyses. For sub-analyses with lesser sample sizes, care was taken interpreting results with the knowledge that significant findings may be missed (ie. committing a type 2 error).

Table 7

Table to show example sample size required for set power and significance levels (271)

Significance level	Assume: Control group response rate =	Effect size: Detect increase in case group at least to:	Power	Sample Size: N needed in each group
0.05 (1 tailed)	30%	40%	0.80	280
	30%	50%	0.80	73
0.05 (2 tailed)	30%	40%	0.80	356
	30%	50%	0.80	92†

† example of sample size accepted for the majority of analyses

Dependent variables for a number of analyses:

AC	n=66 (30 at diag)
HGD	n=25 (14 at diag)
LGD	n=201 (83 at diag)
Dysplasia (all)	n=292 (127 at diag)
HGD/AC*	n=91 (44 at diag)

* majority of analyses

Table 8

Table to show cohort sample sizes for varying analyses

Chapter	Analysis	Sample size (total cohort)
Patient characteristics	Age	1282
	Disease distribution	1282
	Gender	1282
	Weight/BMI	330
	Blood group	380
	Smoking	973
	Alcohol	915
	Co-morbidity	1282
Diagnosis of CLO	Disease distribution	1282
	Length of CLO	746
	Non-confluent disease	1282
	Biopsy number	1282
	Macroscopic lesions	1282
	Biopsy techniques	1282
Helicobacter pylori	Demographics	368
	Disease distribution	368
	Disease severity	368
	Eradication analysis	20
Surveillance of CLO	Demographics	817
	Non surveillance group	453
	Surveillance intervals	1184
	AC survival (surveillance)	35
	AC survival (whole cohort)	65
	Surveillance interval factors	1184
	HGD survival	34

Comparing proportions in 2 groups; example of population size estimation (manual calc)

Calculated from equation:

$$N = \frac{[Pa \times (1-Pa)] + [Pb \times (1-Pb)]}{(Pa-Pb)^2} \times k$$

Pa = proportion with dependent variable, **Pb** = proportion increase/decrease to 'significant level', **Pa-Pb** = effect size, **k** = constant/set number based on p value and power

From whole cohort: Proportion of HGD/AC = 91/1282 = 7% = 0.07
Assuming a 20% change in effect as significant (effect size = 0.2), **Pb** = 0.2 and p values of < 0.05 as significant at 80% (0.80) power [*k* = 7.8]:

$$N = \frac{[0.07 \times (1-0.07)] + [0.2 \times (1-0.2)]}{(0.07-0.2)^2} \times 7.8$$

$$N = 103.9$$

Therefore, approximately 104 patients are required in each group (when HGD/AC vs non HGD/AC is the dependent factor).

Analytical techniques

Data were analysed statistically using SPSS version 11.0 (270)

1. Descriptive data

Descriptive data were examined using SPSS exploratory techniques.
Wherever means were calculated the standard deviation (STD), standard error of the mean (SE) or 95% confidence limits (CI) were also quoted.

2. Inferred data

Distribution of numeric data was examined by plotting histograms and the shape of the curves assessed for appropriateness of parametric or non-parametric testing. For the majority of analyses parametric tests were used where at all possible. Independent T- test and one-way analysis of variance (ANOVA) were used to analyse two and multiple population means respectively.

Chi-Square

The chi-square test of association was used to examine differences between categorical data. It was ensured that data fulfilled the various requirements for use of chi-square analysis as has been previously described (272):

1. The sample must be randomly drawn from the population.

2. Data must be reported in raw frequencies (not percentages);

3. Measured variables must be independent;

4. Values/categories on independent and dependent variables must be mutually exclusive and exhaustive;

5. Observed frequencies cannot be too small.

When cells frequently contained variables that were too low for adequate chi-square testing (<5), the Fisher's exact test was used. When only a few cells were <5 then it was assumed that their contribution to overall significance was negligible, and chi-square analytical values were taken. In contingency tables with more than one degree of freedom it has been shown that the chi-square test is still fairly reliable (273); this was the case for the vast majority of analyses undertaken.

It was also ensured that any observation fell into only one category or value on each variable and that all observations were truly independent.

Odds Ratio (OR)

As this was largely a retrospective observational cohort study where the dependant variable – the presence of disease – was obtained at the time of sampling, and the independent variables were analysed retrospectively, then *Odds Ratios (*OR*)* were calculated when examining relationships between risk factors and outcome.

2 by 2 table used for calculation of OR:

Exposed to risk factor	Group by outcome (eg dysplasia)	
	Cases	Controls
Yes	*a*	*b*
No	*c*	*d*

The odds of exposure to the risk factor amongst those with disease = a/c, and the risk of exposure amongst those without disease ('controls') = b/d. Therefore;

Odds ratio = $\frac{a/c}{b/d} = ad/bc$

Regression (straight line)

Linear regression analysis was done on patient demographic and surveillance data.

Patient demographic chapter:

The age of diagnosis of CLO was examined over time using linear regression assuming the straight line equation:

Y=B0+ mx

Where **Y** = age of diagnosis (=outcome/dependent variable)

m = time of diagnosis (=predictor/independent variable)

B0 = constant coefficient

Surveillance chapter:

Factors affecting surveillance interval were examined using multiple linear regression assuming the following straight line equation, with dependent and independent variables defined below:

$$Y=B0+M1x+M2x+M3x+M4x+M5x+M6x+M7x+M8x$$

Y=surveillance interval
M1= age
M2= grade of disease
M3= presence of oesophageal ulceration
M4= presence of oesophageal stricture
M5= presence of duodenitis
M6= presence of duodenal ulceration
M7= presence of gastritis
M8= presence of gastric ulceration

Survival analyses

Survival data were collected for patients with HGD and AC. On analysis of patients with HGD, effects of early surgery on survival were compared with conservative management and surgery only if AC detected.

The effect of surveillance and detection of AC whilst on surveillance were examined in relation to survival of patients with AC. This was compared with patients whose AC was detected on non-surveillance endoscopies.

For both the HGD and AC analyses, survival tables were constructed and data analysed using Cox regression and log rank analytical models.

Previously documented independent variables that affect survival in AC - age, smoking and co-morbidity (111) - were included as confounding variables.

General Methods of Study

The following data were collected from the database and used in a number of analyses:

Age

The date of birth of all patients, the date of initial diagnosis (when first diagnosed as having CLO or prevalent dysplasia/cancer if appropriate) and the date of detection of worsening disease were all transcribed from the Form 2 to the database and hence age at these stages could be calculated.

Disease classification

'Diagnostic' disease (Δ disease) was taken as disease diagnosed at the first endoscopy when CLO was detected. This may therefore include not only uncomplicated CLO but also prevalent indefinite for dysplasia, low and high-grade dysplasia and AC.

Disease progression was assumed to be as per Figure 1.

'Worst disease' was taken as the most severe endoscopic or histological grade of disease recorded over the follow-up period; and was not, therefore, necessarily the same as disease follow-up endpoint.

'Worst pathology' was defined as the greatest length of CLO documented, the presence of associated oesophagitis, gastritis, duodenitis or gastro-duodenal ulceration at any stage of the patients' follow-up, and the most dysplastic histology noted.

Type of Oesophageal disease was coded initially as follows:

Table 9a Coding grades of oesophageal disease

Classification of disease (diagnosis)	
Barrett's Oesophagus on visual diagnosis only, no histological confirmation (CLO, visual)	1
Columnar-lined oesophagus on histology, no IM (CLO, histo)	2
Columnar-lined oesophagus + IM (CLO, IM)	3
CLO + indefinite dysplasia, no IM documented (CLO, ID)	4
CLO + indefinite dysplasia + IM (CLO, ID + IM)	5
Low Grade Dysplasia (LGD)	6
High Grade Dysplasia (HGD)	7
Adenocarcinoma (AC)	8

For varying analyses categories of disease were recoded as in the Tables below:

Table 9b

Classification of disease	Old code	New code
Non dysplastic CLO	1,2,3	1
Indefinite dysplasia	4,5	2
LGD	6	3
HGD/AC	7,8	4

Table 9c

Classification of disease	Code
Non-Dysplastic CLO (inc ID)	1-5
LGD	6
HGD	7
AC	8

Table 9d

Classification of disease	Old code	New code
HGD/AC	7,8	1
Non HGD/AC	1-6	2

Unless stated otherwise, non-dysplastic CLO (non dysp CLO) included diagnoses of indefinite for dysplasia.

Smoking

Smoking data were recorded and inputted onto the database using the scoring classification shown in the table below:

Table 10a Smoking score

Smoking classification	
1	Never smoked
2	Gave up > 10 years ago
3	Gave up< 10 years ago
4	Current < 20 cigarettes/day
5	Current 20 + cigarettes/day
6	Pipe/cigar or roll up smoker

This is a similar scoring system as used in previous studies (136).

Smoking score was regrouped into the following tables for a number of analyses:

Table 10b

1	Never smoked
2-3	Ex-smokers
4-6	Current smokers

Table 10c

1	Never smoked
2-6	Ever smoked

Analysis was undertaken examining smoking habits at worst diagnosis as a comparison between diagnostic categories.

Alcohol

Alcohol usage was recorded and inputted onto the database having been scored as per the table below;

Table 11a Alcohol score

Score	Males (units/week)	Females (units/week)
1	0-9	0-7
2	10-21	8-14
3	22-40	15-30
4	>40	>30

The scoring system has also been used in prior studies (136). When a numerical value of alcohol units per week was not available for patients then the following scoring system was used when documented:

Table 11b

occasional	1
rarely	1
social	2
moderate	2
heavy	3
excessive	3
alcoholism	4

Alcohol score and disease subtype were examined and comparisons between males and females were analysed.

Co-morbidity

Any significant co-morbidity was documented on the form 2 and entered onto the database. Frequency of the occurrence of various systemic illnesses was analysed per grade of oesophageal disease (worst).

A simple 'co-morbidity score' was calculated based on estimated severity of associated disease and was weighted as follows;

Table 12 Co-morbidity score

Carcinoma (non-oesophageal)	3
Cardiovascular/respiratory disease	2
Other disease	1

Length of columnarised segment

For the majority of the analyses (unless stipulated otherwise) the *total* length of CLO included the presence of non-confluent disease (see Figure 4); ie. if a length of circumferential disease was documented and a coinciding proximal extent of non-confluent disease also recorded then the total length was taken as these two values added together. When length of CLO was documented in patient notes non-specifically as 'extensive' or 'large amounts' for example, then this was inputted numerically onto the database as '99'. However, for analyses where numerical measurements of CLO were estimated, '99' was re-coded as '15 cm', and where categorised into short, intermediate and long segment it was included in the long segment group.

Mean length of CLO was calculated and histograms plotted to examine distribution of the data. Mean lengths of CLO per disease subtype (diagnoses 1-8) were calculated and compared. This was also done with diagnosis re-categorised as per Tables 9b-d. Lengths were also re-classified into the following groups for further analyses:

Table 13a Length of CLO classification

Length of CLO	*classification*
>0≤3 cm	A
>3≤6 cm	B
>6≤9 cm	C
>9 cm	D

Table 13b

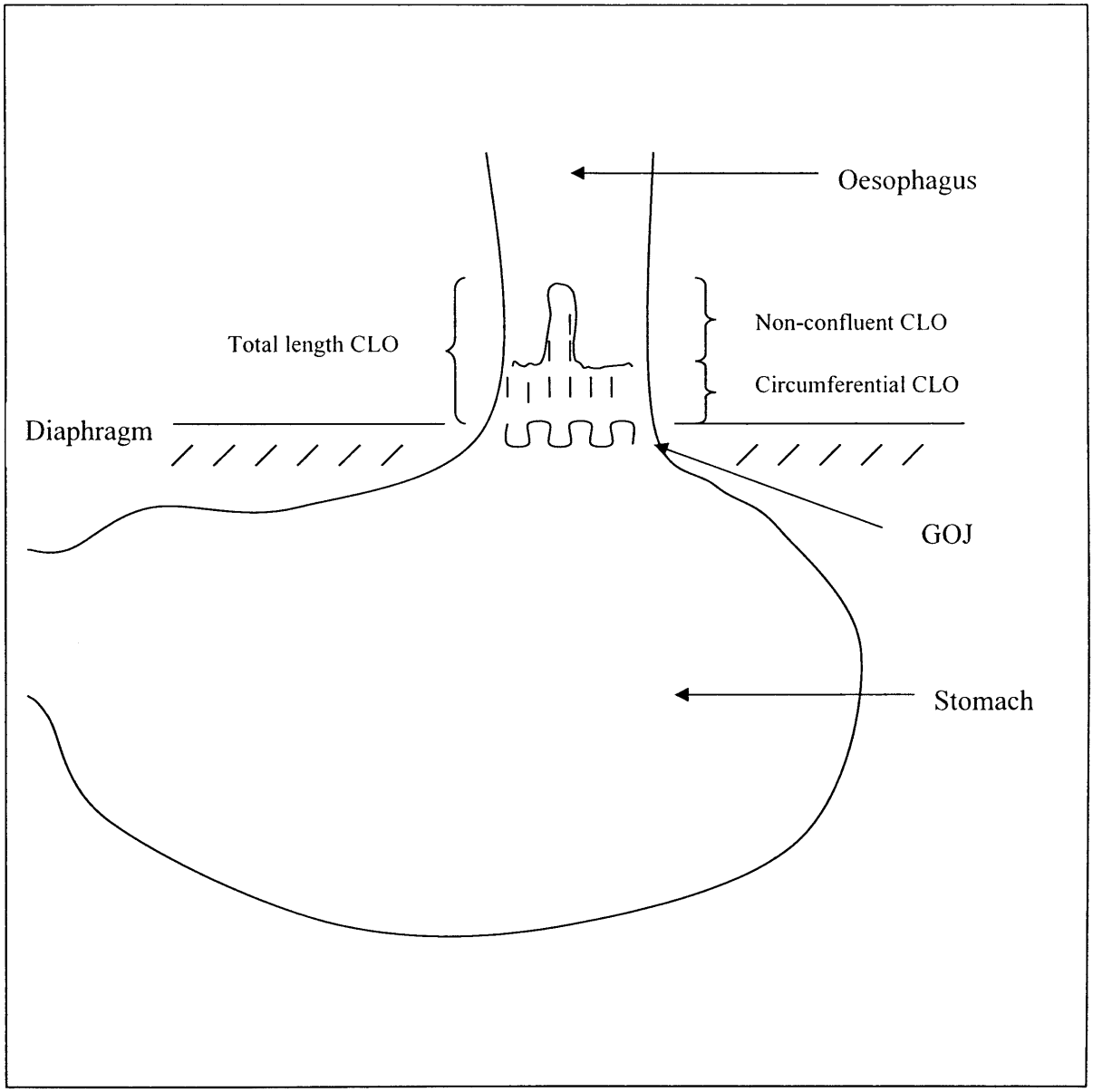
Length of CLO	*Re-classification*
0-3.0 cm	Short Segment Barrett's (SSB)
3.1-6.0 cm	Intermediate Segment Barrett's (ISB)
6.1 cm +	Long Segment Barrett's (LSB)

Table 13c

Length of CLO	*Re-classification*
0-3 cm	Short segment Barrett's
>3 cm	Non-short segment Barrett's

Length of CLO segment was analysed firstly using one-way analysis of variance and then - after regrouping segment lengths into the categories shown previously – using chi square test for association.

Figure 4 Diagrammatic representation of non–confluent and circumferential disease



Specific methods of study

Patient characteristics

Aims

The overall aim was to examine the various patient characteristics and demographics that are associated with CLO and its progression through dysplasia to adenocarcinoma.

Specific patient attributes such as age, gender, blood group, weight, associated co-morbidity and smoking and drinking habits were all examined at all stages of disease in order to isolate some of the factors that might be associated with progression to dysplasia and ultimately adenocarcinoma.

Methods

The cohort consisted of 1282 patients who had been registered with UKBOR between 1996 and 2003, diagnosed with CLO between 27/4/1978 and 17/10/2003, and who had been fully databased. The data incorporated information from six centres (see Table 6)

Specific data were extracted on :

1. Age at initial diagnostic (for CLO) endoscopy (overall mean and means per disease subtype)
2. Age at worst disease endpoint (overall mean and means per disease subtype)
3. Mean age for all prevalent and incident disease
4. Histological disease distribution – At initial diagnosis and worst disease endpoint
5. Patient weight (nearest documented to initial diagnosis when more than one weight recorded)
6. Blood group

7. Smoking habits
8. Alcohol usage
9. Co-morbidity

Age

The age at initial diagnosis of CLO (all disease subtypes together) was examined and analysed for the cohort as a whole and as a comparison between males and females. This was also done for each disease subtype (diagnosed at initial endoscopy).

The age at worst diagnosis (worst histological grade recorded) was examined as above.

Patterns in the age at which CLO was first diagnosed were examined over time, firstly by dividing the cohort into 5 time-bands (see diagnostic chapter) and analyzing using one-way ANOVA; and then using simple linear regression to establish a relationship (see statistical methods).

Disease distribution

Disease distribution was analysed at initial CLO diagnosis by gender and as worst disease diagnosed by gender. Further analysis was undertaken regrouping disease distribution as above.

Patient weight/height/BMI

A large number of weights over a specific period of time were recorded for a number of the patients. When this was the case, the weight nearest to and preceding the patient's diagnosis of CLO was used in the analysis. A comparison was made between mean weights for each specified disease subtype at initial diagnosis and as a comparison between males and females. Disease subtypes were reclassified as above and further analyses undertaken.

It was found that documentation of height was extremely infrequent and it was therefore not possible to calculate sufficient BMIs for adequate, meaningful analyses.

However, 'estimated' BMIs were calculated as follows for a number of sub-analyses:

Patients were grouped into weights correlating to 'overweight' (BMI > 25) and 'obese' (BMI > 30) based on the assumptions that the mean height of the cohort would be similar to that of the general population; ie, 1.75m for men and 1.62m for women (274). This gave predicted weights for 'overweight' and 'obesity' as 77.0 kg and 92.4kg for men respectively; and 65.6 kg and 78.6 kg women (see Table 14).

Table 14 Weight and estimated BMI

Males		**Females**	
≤ 77.0 kg (- overweight)	> 77 kg (+ overweight)	≤ 65.6 kg (- overweight)	> 65.6 kg (+ overweight)
≤ 92.4 kg (- obese)	> 92.4 kg (+ obese)	≤ 78.6 kg (- obese)	> 78.6 kg (+ obese)

BMI = weight (kg)/height^2 (m)

Prior studies performed at UKBOR (136) have suggested that obesity may be a significant risk factor for the development of CLO in young (less than 50 years) people. Analysis was further undertaken, therefore, to ascertain any relationship between weight in people below and above 50 years and the development of dysplastic disease.

Blood Group

Patient's blood groups recorded on the Form 2 were examined and frequencies of each blood group per diagnostic category were analysed.

Diagnosis of CLO

Aims

We aimed to examine variations in practice of diagnosis of CLO over time and also as a comparison between centres in the U.K. We also looked at consistencies in the diagnosis of varying grades of dysplasia and the various techniques employed in distinguishing differences between them.

Of particular interest were:

1. the mean length of CLO diagnosed; with particular emphasis on the diagnosis of short segment disease
2. the frequency in diagnosis of non-confluent disease and its association with various grades of disease diagnosed
3. the number of biopsies taken in diagnosing various stages of disease
4. the presence of macroscopic lesions at diagnosis
5. the use of various biopsy techniques such as '4 quadrant biopsies'

Methods

Part 1

The same cohort was used as for the patient characteristics chapter (see table 6, n=1282).

Specific endoscopic data examined included:

1. length of CLO at diagnosis
2. the presence of non-confluent/circumferential disease (see Figure 5)
3. the presence of macroscopic lesions such as strictures, ulcers or any abnormal mucosal defects
4. the use of biopsy techniques such as '4 quadrant at 2 cm intervals'

Specific histological data examined included:

1. grade of disease
2. number of biopsies taken per diagnosis

The date of diagnosis was noted and patients were grouped into 5 'time-bands' (for a number of the analyses) as per table 15:

Table 15 Classification of Time-bands

Date of Diagnosis	Time-band	Number (n)
1978-1984	1	25
1985-1989	2	136
1990-1994	3	371
1995-1999	4	500
2000 - 2004	5	250

Distribution of disease at diagnosis

The grade of disease at initial diagnosis of CLO - was noted. Grade of disease was coded as indicated previously (see Tables 9a-d).

Length of CLO

The length of the columnarised segment was examined as explained previously. The mean length of CLO diagnosed over the 5 time-bands was also calculated with particular emphasis on frequency of short segment disease diagnosed.

The presence of non-confluent disease

This was examined as a comparison between histological diagnostic groups, and over the 5 time-bands. We sought to examine the hypothesis that patients with complete circumferential disease were more likely to have worse histology *per length*, then those where the total length included non-confluent disease.

Number of biopsies

The number of biopsies taken per initial diagnosis was analysed using one-way anova and subsequent analyses examined changes over the 5 time-bands. The number of biopsies were classified into 4 groups for ease of analysis:

Table 16 Coding for number of biopsies taken

Number of biopsies	Re-coded
0-3	1
4-6	2
7-10	3
11 +	4

'Multiple' biopsies documented on the histology reports were included as group 4.

Macroscopic disease

The presence of strictures, ulcers or any other macroscopic lesions noted at diagnosis were examined and a comparison made between their frequency over time and in relation to the number of biopsies taken.

Biopsy technique

The practice of taking 4 quadrant biopsies as a diagnostic technique was examined over the 5 time-bands.

Part 2

Comparison between centres:

Variations in diagnostic criteria were examined as a comparison between the six centres incorporating the same methods and aims as outlined above.

Helicobacter pylori

Aims

We aimed to examine the association between *H Pylori* status and oesophageal disease severity in a cohort of patients with established CLO registered with UKBOR in a sample of centres spread throughout the U.K.

We specifically aimed to see if length of the Barrett's segment, histological grade of disease and associated presence of oesophagitis were significantly different in the presence or absence of *H pylori* infection. We also aimed to examine frequency of associated gastro-duodenal inflammation/ulceration and to look at the effect of eradication therapy on oesophageal disease.

Methods

Data collection

Data were collected from the same six centres as used in the previous analyses. At the time of the analysis, 1000 patients were fully databased, of which 424 had documented evidence of *H Pylori* status (see Table 17).

Table 17 H Pylori cohort

Centre	Number of patients	HP pos	HP neg
1	104	23	81
2	11	3	8
3	7	4	3
4	25	19	6
5	211	119	92
6	10	10	0

Of these, 66 had evidence of having undergone eradication therapy although 40 had no documentation of *H Pylori* status post treatment. As it was therefore unclear whether or not eradication therapy had been successful in these patients, they were excluded from further analysis. This left three final cohorts:

1) **Helicobacter Pylori positive** (HP pos): n = 178

Patients with documented evidence of *H Pylori* infection on Campylobacter-Like Organism (Clo) test, Breath test, Serology or observed at histology (stomach or oesophagus); and with no subsequent documentation of *H Pylori* negative status were taken as being *H Pylori* positive for the purpose of this study.

Patients who had undergone eradication therapy but who on repeat testing remained *H Pylori* positive (ie. unsuccessful eradication) were also included in this cohort (n=6).

2) **Helicobacter Pylori negative** (HP neg); n = 190

Patients with documented evidence of *H Pylori* negative status on Clo, Breath test or serology were taken as negative for the purpose of the study. Absence of *H Pylori* on histological examination did not qualify for inclusion in the HP neg cohort.

3) **Eradication group** (HP erad); n = 20

Patients with documented evidence of having undergone successful eradication therapy - ie. with documented *H Pylori* positive status prior to eradication and *H Pylori* negative status after treatment (not reverting back to *H Pylori* positive status at any time after the therapy) - were included in the 'eradication group.'

Data extracted

The patients' date of birth, gender, date of diagnosis and length of endoscopic follow-up were all extracted from the database, as was information on smoking and drinking (alcohol) habits. Findings at endoscopy including length of Barrett's segment, presence of associated oesophagitis and presence of gastro-duodenal inflammation or ulceration were also noted. Grade of histology and method of detection of *H Pylori* was also noted. For the majority of analyses, diagnoses 1 and 2 were grouped together (see Table 9a).

Data on smoking and alcohol consumption were extracted in the form of a score as entered on to the database (see Tables 10a-d, 11a+b).

Endoscopic and histological data were extracted for:

a) that present at the time of initial CLO diagnosis (NB: HP erad not included at this stage) and also

b) the worst pathology attained over the follow-up period.

(NB. The worst pathology was always taken after the *H Pylori* status of the patients was defined.)

Surveillance

Aims

The overall aim was to examine the practice of endoscopic and histological surveillance for Barrett's CLO - and its progression through dysplasia to adenocarcinoma - in a sample of hospitals fairly evenly spread throughout the U.K.

We sought to examine whether surveillance programmes detected cancers at an early and treatable stage; what the best surveillance interval was in order to achieve this, whether specific endoscopic and biopsy techniques were employed and if they had any influence on detection rate, and consistency in practice between different centres.

Specific aims included examination of:

1. Surveillance programme enrolment:

a. The proportion of patients with a diagnosis of CLO selected for surveillance and the various criteria used for basing this selection.

b. The criteria/reasons for excluding patients from surveillance programmes

2. Surveillance interval:

a. The mean endoscopic interval whilst under surveillance for each histological stage of disease.

b. The 'detection rate'/ number of dysplasias or cancers diagnosed over the follow-up period for patients being surveyed at specific intervals.

c. Factors that affect surveillance interval other than grade of disease itself

3. Surveillance practice:

a. Number of biopsies taken at endoscopy

b. Use of various types of forceps and employment of specific biopsy techniques (particularly incorporation of a '4 quadrant biopsy technique')

c. Management of HGD/AC

d. Documentation of length of CLO/measurement and GOJ/SCJ level at endoscopy
e. Presence of oesophagitis at endoscopy
f. Test for Helicobacter Pylori

The same cohort as for the patient characteristics and diagnostic study were used (see Table 6, n=1282).

Specific data were extracted on:
a. Enrolment onto a surveillance programme
b. Reasons for excluding patients from surveillance
c. Demographic and intrinsic patient factors
d. Endoscopic findings on surveillance
e. Histological findings from surveillance biopsies
f. The surveillance (endoscopic) interval employed
g. The rate of detection of dysplasia and adenocarcinoma whilst on surveillance
h. The endoscopic biopsy technique employed at surveillance endoscopies
i. Outcome/ patient survival

The data were analysed, firstly overall incorporating information from all of the centres; then as a comparison between centres.

Demographic data

The age of the patient at diagnosis of their CLO was extracted and means for the entire cohort and per centre were calculated. Gender distribution was examined and male:female ratios calculated for all of the centres and compared.

Co-morbidity

Details of associated patient co-morbidity was extracted from the database and used for the AC and HGD survival analysis.
The co-morbidity score described earlier was used in the analyses.

Oesophageal disease was classified as done for previous analyses (see Tables 9a-d).

Endoscopic data

Each endoscopy report was previously coded (on databasing of Form 2) so that the reason for performing the endoscopy was apparent.

The first endoscopy diagnosing CLO was coded '**D**' for diagnostic.

Surveillance endoscopies were coded '**S**', and were noted for endoscopies where a diagnosis of CLO had been previously made and that had documented evidence that they were being done as part of a surveillance programme and for no other reason.

Endoscopies done for *new symptoms* whilst on surveillance were coded as '**N**'.

Endoscopies done for new symptoms in patients who had no documented evidence of being in surveillance programmes were coded as '**W**'. Endoscopies done post-oesophagectomy were coded as '**P**'.

Any other factors that were thought to influence surveillance intervals other than the type of Barrett's epithelium being examined were noted. These included the presence of oesophageal strictures at endoscopy, oesophageal ulceration and the presence of associated upper GI pathology such as gastritis, duodenitis or gastric or duodenal ulceration.

The length of the Barrett's segment and whether or not the disease was circumferential or non-confluent, was noted from the report.

If the disease was documented as circumferential with a proximal extension of non-confluent disease, then this last measurement was taken as the proximal extent of the segment (see Figure 5).

Histological data

Diagnosis of oesophageal disease was taken as documented in the histology reports from the various centres.

Diagnoses were grouped as per Table 1 and subtracted from the database in this format for analysis.

The number of biopsies taken at each diagnosis were noted as was the practice of specific techniques, such as *four quadrant biopsies* or the use of jumbo forceps, if stated on the histology (or endoscopy) report.

Surveillance programmes

Patients were only included in the *surveillance group* if there was documented evidence that they had been entered into a surveillance programme. If this was not the case, it was assumed that they were undergoing endoscopic examination for another reason, and that reason was documented if evident. If just a single diagnostic endoscopy had been performed then these patients were *not* included in the surveillance cohort. Reasons for not being entered into a surveillance programme – such as 'age', 'co-morbidity', 'patient choice' or 'patient moved from area' - were also recorded if present.

Endoscopic (Surveillance) interval

The number of endoscopies performed over a specific time period allowed endoscopic interval to be calculated. The interval after each endoscopic/histological event resulting in a specific diagnosis was calculated.

If the patient's diagnosis changed over the follow-up period then the calculated intervals took this into account, and the interval prior to these changes were documented. For example, any event resulting in a diagnosis of 2 (CLO on OGD with histological confirmation) whether at initial diagnostic endoscopy or detection on follow up endoscopy was documented and the subsequent endoscopic interval (prior to the next endoscopic event) was recorded. Therefore, endoscopic intervals for one patient may be included for several disease sub-types.

Mean endoscopic intervals were calculated for all disease types 1 – 7; and recalculated after regrouping disease (Tables 9a-d).

Separate analyses were done examining the proportion of endoscopies done specifically for surveillance (ie. not for 'new symptoms' or 'follow-up for other reasons').

Data were examined using SPSS exploratory techniques and histograms plotted to examine the shape of the distribution curve in order to assess suitability for parametric testing. Comparison between the means was undertaken using one-way analysis of variance

Detection of worsening disease

Any progression of disease detected during the period of surveillance was noted, as was the indication for the endoscopy done at the time (ie. surveillance only, new symptoms whilst on surveillance etc)

The sequence of disease progression used is demonstrated in Figure 1. Regression of disease, if present, from a diagnosis of indefinite dysplasia, low-grade dysplasia or high-grade dysplasia was noted.

Patients were grouped into surveillance for specific grades of disease (diagnoses 1-7) and by endoscopic interval (see below).

The numbers of patients developing worsening dysplastic disease ($\geq$ diagnosis 6) over the follow-up period in each endoscopic interval group was noted and statistical analysis of differences between the groups undertaken using chi-square test of association.

Endoscopic interval was recoded for the purpose of this analysis as follows:

Table 18 Endoscopic interval coding

Endoscopic interval	
$\leq$ 3 months	A
>3$\leq$6 months	B
>6$\leq$12 months	C
>12$\leq$18 months	D
>18$\leq$24 months	E
>24 months	F

HGD/AC analysis

HGD and AC were dealt with separately and management of patients with these grades of disease examined closely.

Treatment

If a patient underwent interventional therapy such as laser, photodynamic therapy or oesophagectomy then this was documented.

Survival

Documentation of outcome was noted. Patient survival was calculated from a start-point – either histological diagnosis of HGD or AC - to either the last documented event in the notes (eg. consultation, endoscopic examination, surgery..) if alive (ie. censored to the point of follow-up), or to the point at which it is documented that the patient died; evident either from entrance in the notes or from information transcribed from the death certificate. Survival data were analysed as described previously in the statistical analyses section.

Endoscopist survey

A questionnaire was designed to examine current practices for the management of CLO and its complications. It aimed to look at aspects of endoscopic and histological criteria for the diagnosis of CLO and current practice of surveillance (see Appendix 4).
The questionnaire was divided into 3 parts; A, B and C. Part A incorporated questions pertaining to the use and availability of a specific policy for the management of CLO if applicable; part B examined various criteria for the diagnosis of CLO and part C looked at surveillance practice. It encompassed 13 questions subdivided into a total of 53 subsections. 83% of these sections were structured in a 'tick box' format with 79.5% of them asking for a 'yes/no' response. The remaining 17% of subsections asked for a 'freehand' response, mainly in the form of a one-word answer.

Questionnaires were sent to endoscopists at 41 centres spread throughout England, Scotland and Wales (see Figure 1). All centres had registered with UKBOR and either had patients already on the database or were in the process of registering patients. Questionnaires were sent between February and April 2004, and all replies were received by September of that year.
The questionnaires were sent out on behalf of UKBOR and were accompanied by a letter explaining their purpose and ensuring anonymity of participants.
A follow up letter was sent to all centres within 3 months either thanking them for their participation or encouraging them to do so if no replied had as of yet been received.

Responses from the lead endoscopists from each of the centres were identified and enabled a separate analysis examining their particular practice to be performed. Identification of the centres and individuals remained anonymous.

Results

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Patient characteristics

Age at initial diagnosis

The mean age at initial diagnosis - first diagnostic OGD for CLO, all grades of disease included - for the entire cohort was 62.7 years (STD 13.95; SE 0.390; 95% CI 61.90-63.43), with mean age for females being 66.43 years (STD 12.99; SE 0.59) (95%CI 65.25-67.58) and males 60.39 years (STD 14.03; SE 0.50) (95% CI 59.42-61.37).

On statistical analysis, men are significantly younger than women ($p<0.001$, indep T-test) (see Figure 5).

Mean ages for each disease subtype (males and females combined) at initial diagnosis were calculated and are presented below:

Table 19a Mean age for grades of disease at initial diagnosis

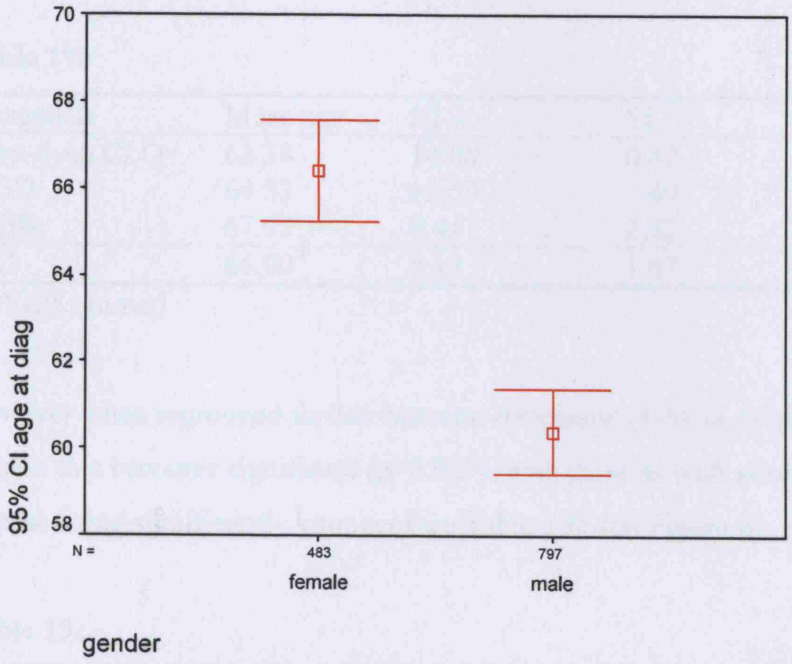
Initial diagnosis	Mean age	STD	SE mean
CLO (visual)	63.05	13.76	0.69
CLO (histo)	62.41	14.45	0.96
CLO (IM)	62.49	13.48	0.66
CLO (ID)	60.01	14.74	2.84
CLO (ID+IM)	62.74	12.70	1.56
LGD	64.53	13.59	1.49
HGD	67.99	9.44	2.52
AC	66.00	9.13	1.67

P=0.468 (one-way anova)

On one-way anova there are no statistically significant differences between mean age at diagnosis for the various disease subtypes shown in the table above ($p=0.468$).

When disease subtypes are reclassified into non-dysplastic CLO, indefinite dysplasia (ID) and dysplasia/AC there is a trend towards patients with dysplastic disease being slightly older; but this does not quite reach significance ($p=0.070$).

Fig 5 Error bars to show mean age at initial diagnosis of CLO between males and females



There remains no significant differences when disease is regrouped into non-dysplastic CLO (including indefinite for dysplasia), LGD, HGD and AC (p=0.125; one-way anova) (see Table 19b).

Table 19b

Diagnosis	Mean age	STD	SE	95% CI
Non-dysp CLO	62.38	14.08	0.42	61.56-63.19
LGD	64.53	13.59	1.49	61.56-67.50
HGD	67.99	9.44	2.52	62.54-73.44
AC	66.00	9.13	1.67	62.59-69.41

P=0.125 (anova)

However when regrouped further into non-dysplastic (1-5) vs dysplastic (6-8) disease this becomes significant (p=0.027), with patients with non-dysplastic disease being significantly younger (see Table 19c and Figure 6).

Table 19c

Diagnosis	Mean age	STD	SE	95% CI
Non-dysp CLO (1-5)	62.38	14.08	0.42	61.56-63.19
Dysp CLO (6-8)	65.26	12.24	1.09	63.11-67.41

P=0.027 (indep T) (95% CI: -0.54- -.33)

Age at worst disease

433 (33.8%) patients developed worsening disease. In these patients, the mean age at diagnosis of worst disease was 64.1 years (STD 12.35; SE 0.59; 95% CI 62.88-65.21).

There were significant differences in mean age at worst disease diagnosed per each disease subtype (p=0.025), with patients developing AC significantly older (p=0.001 on indep T: AC vs non AC; 95% CI: -11.66- - 3.2) (see Table 20 and Figure 7)

Fig 6 Error bars of mean age at diagnosis of non-dysplastic and dysplastic disease

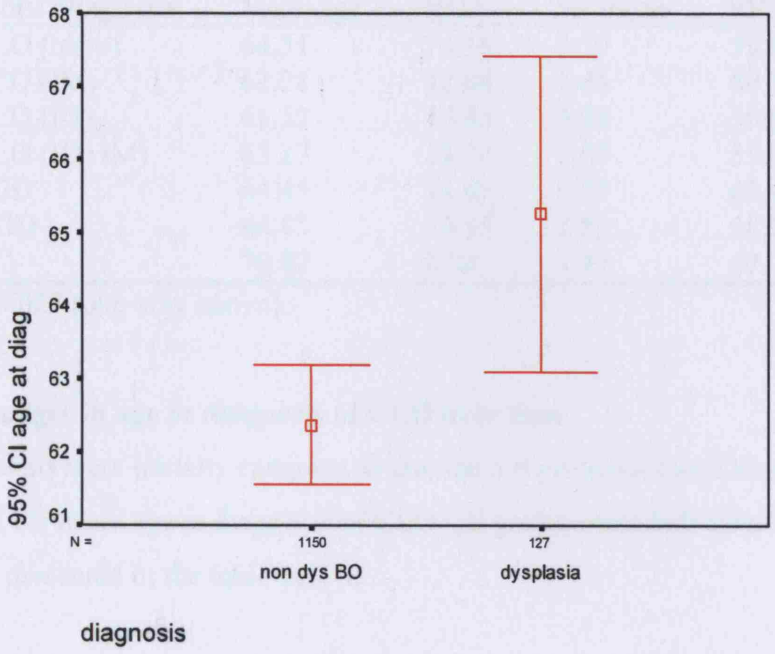


Figure 7 Means plot of age at worst diagnosis for all grades of disease

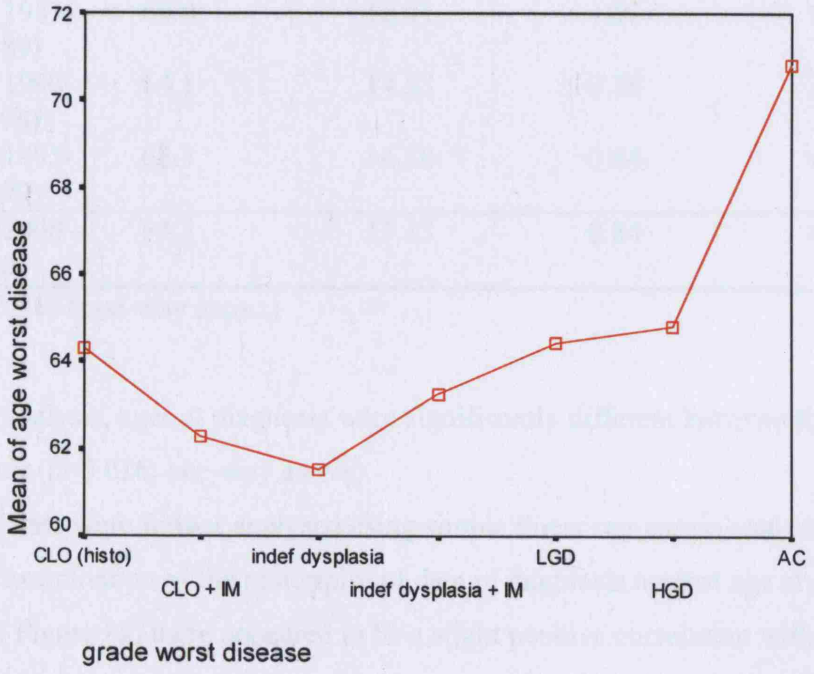


Table 20 Mean age at worst disease endpoint

Worst Diagnosis	Mean age	STD	SE mean	95% CI
CLO (histo)	64.31	14.16	2.39	59.45-69.18
CLO (IM)	62.28	12.84	1.06	60.18-64.38
CLO (ID)	61.52	14.93	4.98	50.04-73.00
CLO (ID+IM)	63.27	13.34	1.64	59.99-66.55
LGD	64.45	11.02	0.99	62.49-66.41
HGD	64.83	10.95	2.83	58.77-70.89
AC	70.82	8.84	1.49	67.78-73.86

P=0.025 (one-way anova)

Changes in age at diagnosis of CLO over time

Patients were initially categorised into the 5 time-bands (see Diagnosis chapter) and the mean age at diagnosis of CLO (all grades included) calculated. The results are presented in the table below:

Table 21 Mean age at initial diagnosis between the time-bands

Timeband	Mean age (years)	STD	SE mean	95% CI
1 (1978-1984)	58.0	9.20	1.84	54.3-61.9
2 (1985-1989)	60.0	12.41	1.06	57.9-62.1
3 (1990-1994)	64.1	14.57	0.76	62.6-65.6
4 (1995-1999)	62.3	14.38	0.64	61.1-63.6
5 (2000 – 2004)	63.3	13.33	0.84	61.7-65.0

P=0.016 (one-way anova)

On analysis, ages at diagnosis were significantly different between the 5 time-bands (p=0.016, one-way anova).

The data were further analysed using simple linear regression analysis.

On examination of the scatterplot of date of diagnosis against age at diagnosis (see Figure 8a) there appeared to be a slight positive correlation with patients in more recent years being diagnosed at a slightly older age, however, this did not

quite reach statistical significance (p=0.091, Pearson correlation) [Multiple correlation coefficient (R) = 0.045; R square = 0.002; adjusted R square = 0.001; T (test of reg coefficient for significance) = 1.69; p (associatewith t) = 0.091].
Linear regression was repeated dividing the cohort into non-dysplastic (diagnoses 1-5) and dysplastic disease (diagnoses 6,7).
For both, scatterplots (see Figures 8b,c) suggested a trend towards a positive correlation again, however neither reached statistical significance (p=0.133, Pearson correl : non-dysp) (p=0.463, Pearson correl : dysp) (Figures 9b,c).
Non-dysplastic disease : [R = 0.45; R square = 0.002; adjusted R square = 0.001
T= 1.502; p vale = 0.133].
Dysplastic disease: [R = 0.066; R square = 0.004; adjusted R square = -0.004
T= 0.737; p= 0.463].

Figure 8a Scatterplot of date of diagnosis of CLO against age at diagnosis (all grades of disease)

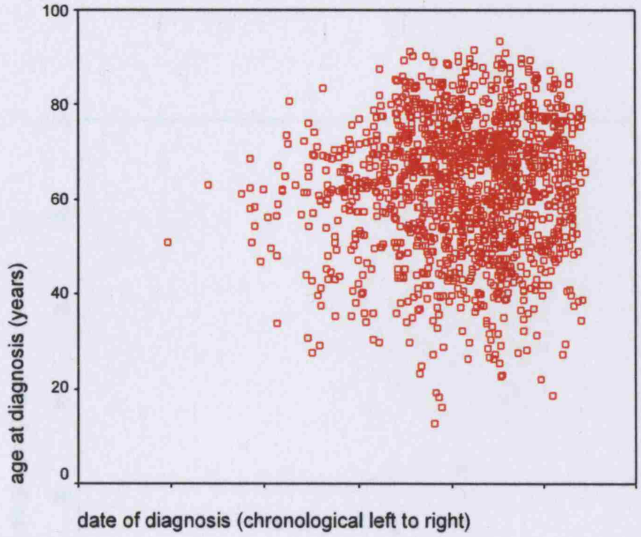


Figure 8b Scatterplot of date of diagnosis against age at diagnosis (non-dysplastic CLO)

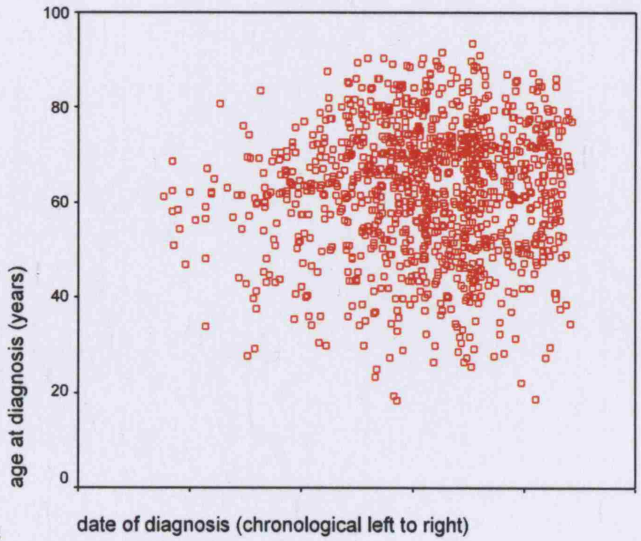
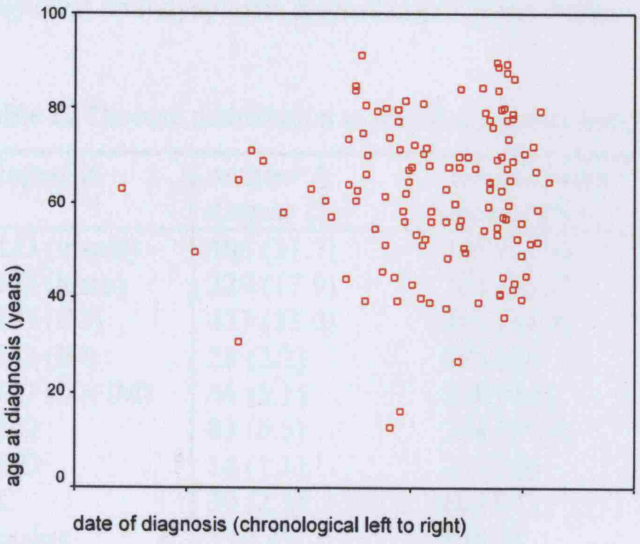


Figure 8c Scatterplot of date of diagnosis against age at diagnosis (dysplastic disease)



Disease distribution

At initial diagnosis 1152 (89.9%) patients had evidence of non-dysplastic disease (diagnosis 1-5) and 127 (9.9%) dysplastic disease (diagnoses 6-8). At worst disease endpoint 985 (76.8%) had non-dysplastic CLO with 292 (22.8%) being diagnosed with dysplastic disease (see Figures 9a/b).

Table 22 Disease distribution at initial diagnosis and worst disease

Diagnosis	number Δ disease (%)	number worst disease (%)
CLO (visual)	406 (31.7)	145 (11.3)
CLO (histo)	229 (17.9)	201 (15.7)
CLO (IM)	423 (33.0)	493 (38.5)
CLO (ID)	28 (2.2)	26 (2.0)
CLO (ID+IM)	66 (5.1)	120 (9.4)
LGD	83 (6.5)	201 (15.7)
HGD	14 (1.1)	25 (2.0)
AC	30 (2.3)	66 (5.1)
missing	3 (0.2)	5 (0.4)
Total	1282	1282

On grouping of worst diagnosis into prevalent and incident disease, the following table was produced: (see Figure 10)

Table 23 Disease distribution at worst pathology; prevalent and incident

Diagnosis	Prevalent	Incident	Total
CLO (visual)	145	0	145
CLO (histo)	179	22	201
CLO (IM)	395	98	493
CLO (ID)	21	5	26
CLO (ID+IM)	73	47	120
LGD	101	100	201
HGD	17	8	25
AC	41	25	66
Total	972	305	1277

54.5% of all dysplastic disease was classified as prevalent disease; with 50.2% of LGD, 68% of HGD and 62.1% of AC being diagnosed within 1 year of initial diagnosis of CLO.

A total of 66 (5.2%) patients were diagnosed with AC over the entire follow-up period. 30 cancers were diagnosed at first diagnostic (for CLO) endoscopy (2.3% of cohort), with a further 11 (0.9%) diagnosed within 1 year, making a total of 41 (3.2%) prevalent ACs.

25 (2.0%) patients developed incident AC.

Figure 9a distribution of disease at initial diagnosis

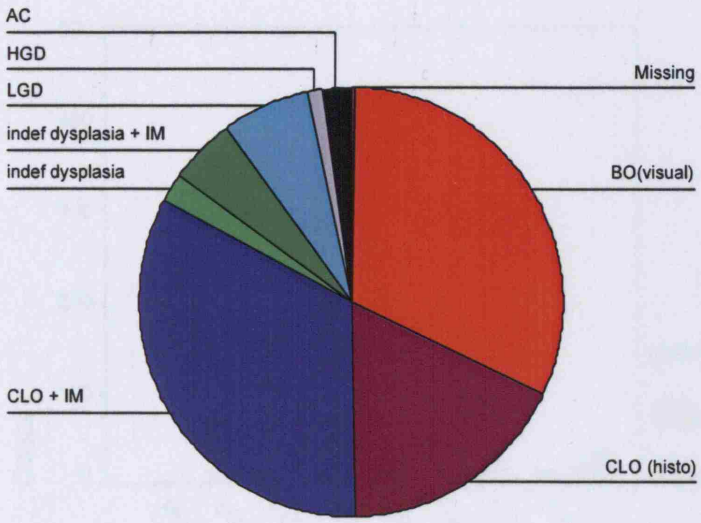


Figure 9b distribution of disease at worst diagnosis

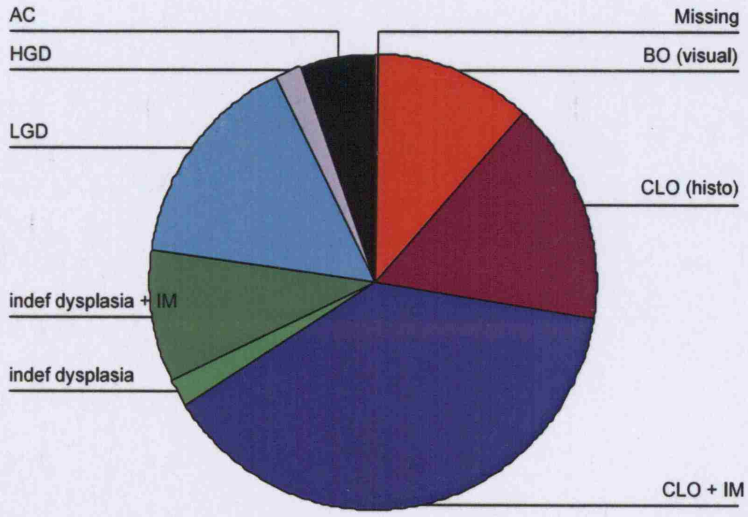
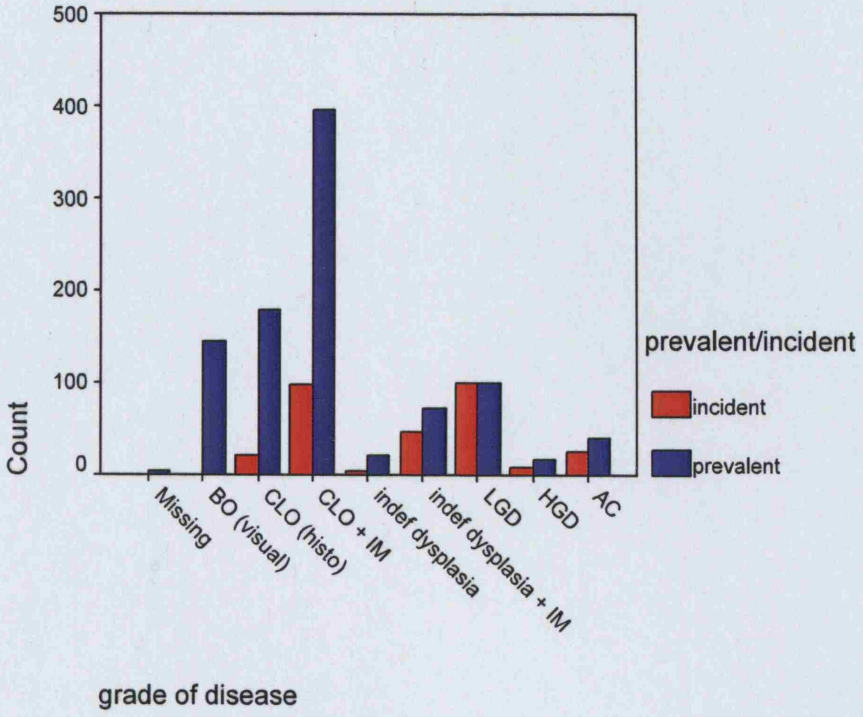


Figure 10 Distribution of worst disease; prevalent and incident



Gender

The male to female ratio for the entire cohort at initial diagnosis (all disease subtypes included) was 1.65:1 (797:482). The gender distributions for each disease subtype - at initial diagnosis and worst disease - are presented in the tables below: (see Figures 11a,b)

Table 24a Gender distribution of disease at initial diagnosis

Initial Diagnosis	**Gender**		
	Male	Female	Ratio (M:F)
CLO (visual)	244	162	1.51:1
CLO (histo)	138	91	1.52:1
CLO (IM)	270	153	1.76:1
CLO (ID)	12	16	0.75:1
CLO (ID+IM)	47	19	2.47:1
LGD	52	31	1.68:1
HGD	10	4	2.5:1
AC	24	6	4:1

Table 24b Gender distribution of disease at worst pathology

Worst Diagnosis	**Gender**		
	Male	Female	Ratio (M:F)
CLO (visual)	78	67	1.16:1
CLO (histo)	112	89	1.26:1
CLO (IM)	314	179	1.75:1
CLO (ID)	13	13	1:1
CLO (ID+IM)	85	35	2.43:1
LGD	127	74	1.72:1
HGD	19	6	3.17:1
AC	47	19	2.47:1

There is a higher proportion of males in all groups except for diagnosis 4 (indefinite for dysplasia, no IM), where numbers are very small.

There is also a trend towards a higher male:female ratio for dysplastic disease, both at initial and worst diagnosis. For AC, however, there appears to be a much higher ratio of males to females on initial diagnostic OGD (4:1), when compared to the corresponding ratio at worst diagnosis (2.47:1).

On statistical analysis there is a significant difference between gender distribution ratios and disease subtype (p=0.011); although, on regrouping disease into non-dysplastic CLO (1-5) and dysplastic CLO (6-8) - despite a trend in a higher proportion of males in the dysplastic CLO group - these significant differences are not seen (p=0.123).

On regrouping again into HGD/AC and non HGD/AC there is, however, a significant difference in the male:female ratio (p=0.036) with an increasing preponderance of males developing HGD/AC.

Table 25 Gender distribution at worst pathology; non-HGD/AC vs HGD/AC

Worst diagnosis	**Gender**		
	Male	Female	Ratio
Non-HGD/AC	729	457	1.60:1
HGD/AC	66	25	2.64:1
	795	482	

P=0.036 (chi-square)

When disease is regrouped into prevalent and incident disease (NB*: at worst diagnosis*) the following ratios are obtained:

Table 26a Gender distribution at worst pathology

Prevalent disease	**Gender**		
	Male	Female	Ratio
Non HGD/AC	557	357	1.56:1
HGD/AC	44	14	3.14:1

P=0.015 (chi-square)

Table 26b

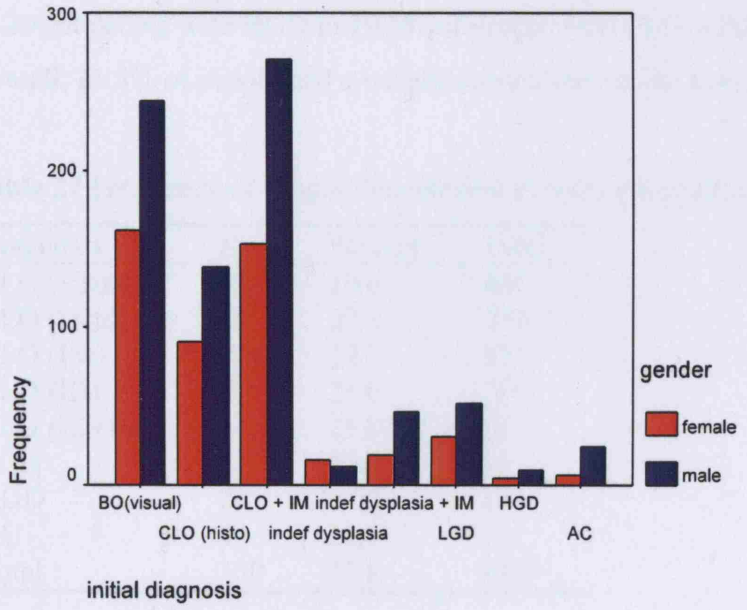
Incident disease	**Gender**		
	Male	Female	Ratio
Non HGD/AC	172	100	1.72:1
HGD/AC	22	11	2:1

P=0.699 (chi-square)

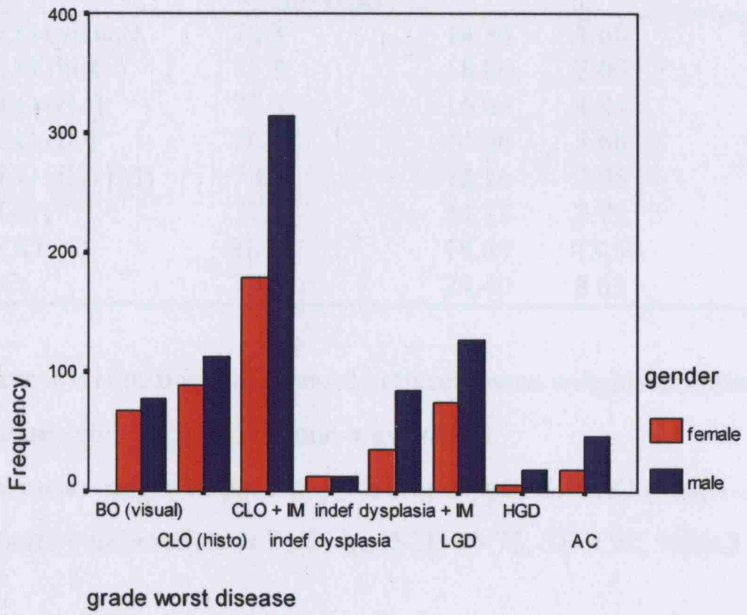
There is, therefore, a significant difference in male:female ratio when proportions of HGD/AC are compared with non HGD/AC for prevalent disease (p=0.015, chi-square), but not for incident disease (p=0.699, chi-square).

Figures 11 a, b Gender distribution of cohort

a) Gender distribution at all grades of disease at initial diagnosis



b) Gender distribution at all grades of disease at worst diagnosis



Weight

The weights of patients at initial diagnostic endoscopy were analysed.

The frequency of documentation of weight varied depending on diagnosis, from 14.3% of people with HGD to 29.3% of people with CLO + IM (see Table 27).

Overall, 25.8% of people had a weight documented in the notes.

Table 27 Frequency of weight documented in notes per grade of disease

Diagnosis	N	Percent	Total
CLO (visual)	81	20.0	406
CLO (histo)	64	27.9	229
CLO (IM)	124	29.3	423
CLO (ID)	7	25.0	28
CLO (ID+IM)	17	25.8	66
LGD	27	32.5	83
HGD	2	14.3	14
AC	8	26.7	30
Total	330	25.8	1279

The mean weights of patients per grade of disease diagnosed are presented in Table 28.

Table 28 Mean weights of patients per grade of disease

Diagnosis	Mean weight (Kg)	STD	SE mean	95% CI
CLO (visual)	70.8	14.34	1.60	67.6-73.9
CLO (histo)	73.8	18.86	2.09	69.6-78.0
CLO (IM)	77.3	16.04	1.44	74.4-80.1
CLO (ID)	76.9	14.96	5.66	63.0-90.7
CLO (ID+IM)	79.9	12.16	2.95	73.6-86.1
LGD	77.7	14.13	2.72	72.1-83.2
HGD	83.5	19.09	13.50	-88.0-255
AC	75.0	24.40	8.63	54.63-95.42

There is a significant difference between mean weights at initial diagnosis per disease subtype (p=0.048, one-way anova).

The mean weight of patients with non-dysplastic CLO (diag 1-5, males and females combined) was 74.86 kg (STD 15.75, SE 0.92, 95%CI 73.05-76.67).

The mean weight (males and females combined) for HGD/AC was 69.37 kg (STD 10.25; SE 2.65), and for non HGD/AC was 74.92 kg (STD 14.87; SE 0.85) with no significant difference between them (p=0.154, indep T test).

The mean weights for males and females analysed separately are presented in the table below:

Table 29 Mean weight in kg at initial diagnosis – a) males b) females

a) Males

Diagnosis	*Weight*	*STD*	*SE mean*	*95% CI*
CLO (visual)	73.6	12.90	1.90	69.8-77.4
CLO (histo)	80.7	12.53	1.96	76.7-84.7
CLO (IM)	81.3	13.98	1.59	78.1-84.4
CLO (ID)	80.2	23.02	13.29	23.1-137.4
CLO (ID/IM)	83.5	11.08	3.07	76.8-86.4
LGD	79.6	13.13	3.19	72.9-86.4
HGD	97.0*	na	na	na
AC	68.3	6.66	2.72	61.3-75.3

b) Females

Diagnosis	*Weight*	*STD*	*SE mean*	*95% CI*
CLO (visual)	66.9	15.44	2.65	61.5-72.3
CLO (histo)	62.0	16.97	3.46	54.8-69.2
CLO (IM)	70.8	17.18	2.51	65.7-75.8
CLO (ID)	74.4	8.66	4.33	60.6-88.2
CLO(ID/IM)	68.0	7.22	3.1	56.5-79.5
LGD	74.3	15.81	5.00	63.0-85.6
HGD	70.00*	na	na	na
AC	95.2	53.53	37.85	-385.8-576.1

* one patient only

Table 29c Mean weight for uncomplicated CLO (Δ1-5) at initial diagnosis

	Mean weight	STD	SE mean	95% CI
Males	79.32	13.63	1.02	77.32-81.34
Females	67.76	16.30	1.54	64.72-70.81

Table 29d Mean weight for Non HGD/AC vs HGD/AC – males & females

	Females			*Males*		
Diagnosis	**Weight**	**STD**	**SE mean**	**Weight**	**STD**	**SE mean**
Non - HGD/AC	68.85	14.36	1.33	78.56	13.99	1.01
HGD/AC	68.20	8.40	3.43	70.14	11.75	3.92

Results of weight and age distribution analysis

Patients were divided into <50 years and those ≥ 50 years and also into a specific weight category as based on assumed BMIs for 'overweight' and 'obesity' (see methods). The cohort was divided into males and females and proportions of non-dysplastic (diagnoses 1-5) to dysplastic disease (diagnoses 6-8) were analysed using chi-square, with the following results:

In males under 50 years, there were no significant differences in proportions of non-dysplastic to dysplastic disease for patients less than or greater than 77.0kg (+/-'overweight') (p=0.115); nor less than or greater than 92.4 kg (+/-'obese') (p=0.109).

This was also true for males over 50 years, with proportions of non-dysplastic to dysplastic disease similar for +/- 'overweight' (p=0.529) and +/- obese (p=0.988).

In females under 50 years there were also no significant differences in proportions of non-dysplastic to dysplastic disease in the +/- 'overweight' (p=0.710) nor +/- 'obese' (p=0.410) categories. This remained true in females over the age of 50 (+/- overweight, p=0.164; +/- obese, p=0.103).

Analysis was redone classifying patients into either 'normal weight' (ie less than 77.0 kg for men and less than 65.6 kg for women) or 'obese (ie greater than 92.4 kg for men and 78.6 kg for women).

In males under 50 years there was a trend towards a higher number of obese males developing dysplastic disease with an odds ratio of 7.27; however on chi-square analysis this did not reach significance (p=0.061) (Fisher exact p=0.084)

Table 30a Proportions of dysplastic disease in obese and non-obese males <50y

Males < 50	dysplasia	no dysplasia
Obese	4	11
Normal weight	1	20

In males over 50 years there was no evidence of such a trend (p=0.876).

Table 30b Proportions of dysplastic disease in obese and non-obese males >50y

Males > 50	dysplasia	no dysplasia
Obese	5	12
Normal weight	26	57

In females both under and over 50 years there were no significant differences in proportions of non-dysplastic to dysplastic disease (p=0.764, Fisher exact; and p=0.194, chi; p=0.228, Fishers exact) respectively.

On reclassifying disease into non HGD/AC and HGD/AC there remained no significant differences in females (p=0.333, Fishers exact, < 50; p=0.803, Fishers exact, > 50), or males (< 50 ; no stats as no HGD/AC; > 50 p=0.525, Fishers exact).

Blood Group

380 (29.6%) patients had evidence of documentation of their blood group in the notes. Distribution of blood group is presented in the table below (see Figure 12):

Table 31 Distribution of blood group in cohort

Blood group	frequency	percentage
A-	29	2.3
A+	131	10.2
AB+	9	0.7
B-	5	0.4
B+	26	2.0
O-	36	2.8
O+	144	11.2
missing	902	70.4
Total	1282	100.0

On chi-square analysis; there are significant differences in blood group distribution between the disease subtypes (grades 1 to 8) (p=0.011)
When disease is regrouped into non-HGD/AC and HGD/AC the following table is produced (Table 32):

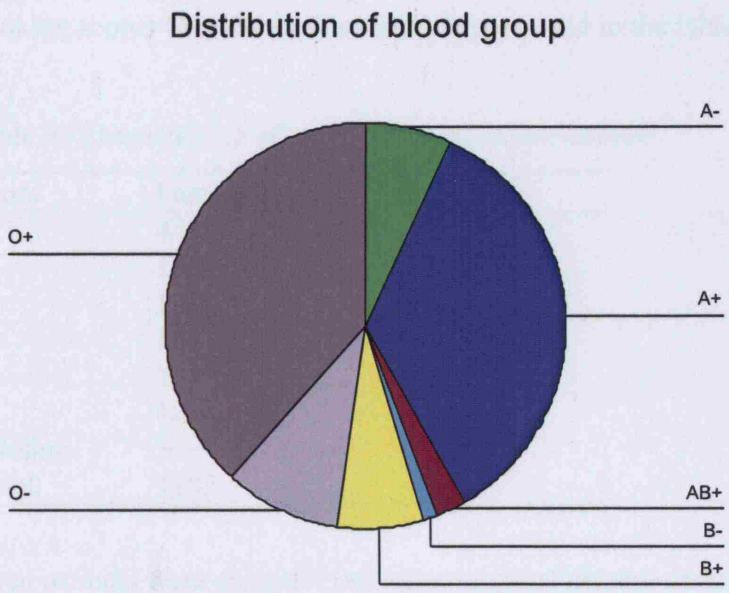
Table 32 Distribution of blood group in dysplastic and non-dysplastic disease

	Blood group						
Diagnosis	A+	A-	AB+	B+	B-	O+	O-
Non HGD/AC	119	24	8	22	5	132	26
HGD/AC	12	26	1	4	O	12	10*

P=0.037 (chi-square)

*On more detailed analysis, it appears that in patients who are O- there are significantly higher proportions of HGD/AC compared with proportions of HGD/AC in all other blood groups combined (p=0.001, chi-square).

Figure 12 Distribution of blood group



Smoking

Information on smoking habits was available in 973 (75.9%) patients.

Smoking scores for the whole cohort are presented in the table below:

Table 33 Frequency of smoking score for entire cohort

Score	Frequency	Percentage
1	445	34.7
2	133	10.4
3	131	10.2
4	103	8.0
5	145	11.3
6	16	1.2
Missing	309	24.1
Total	1282	100.0

When patients were grouped into worst grade of disease documented and smoking scores compared, there were no overall significant differences (p=0.072, chi-square) (see Table 34a).

Table 34a Smoking scores for disease regrouped by worst pathology

	Smoking score					
Diagnosis	1	2	3	4	5	6
CLO (visual)	45	10	15	12	20	2
CLO (histo)	80	20	23	9	14	2
CLO (IM)	162	39	56	35	59	5
CLO (ID)	13	3	3	3	2	0
CLO (ID+IM)	47	19	7	10	14	2
LGD	79	26	16	21	21	4
HGD	6	4	0	4	4	0
AC	12	12	11	9	11	1
Total	444	133	131	103	145	16

P=0.072 (chi-square)

When worst disease was regrouped into non-HGD/AC vs HGD/AC, there were significant differences in proportions of disease per smoking score (p=0.004, chi-square) (see Table 34b).

Table 34b Smoking score and proportions of non-HGD/AC to HGD/AC

	Smoking score					
Diagnosis	1	2	3	4	5	6
Non-HGD/AC	426	117	120	90	130	15
HGD/AC	18	16	11	13	15	1

P=0.004 (chi-square)

On further analysis there were significantly higher proportions of HGD/AC observed in patients who had 'ever smoked' (scores 2-6) compared to those who had 'never smoked'(score 1) (OR 2.81; p<0.001, chi-square) (see Table 34c) and in patients who were current smokers compared to those who were ex-smokers or had never smoked (OR 1.88; p=0.012, chi-square) (see Table 34d).

Table 34c

Smoke status	HGD/AC	Non HGD/AC
Ever smoked	56	472
Never smoked	18	426

P<0.001 (chi-square) OR = 2.81

Table 34d

Smoke status	HGD/AC	Non HGD/AC
Current	28	220
Ex/never	45	663

P=0.012 (chi-square) OR = 1.88

There were no significant differences in proportions of HGD/AC to non-HGD/AC between patients who were current smokers compared with patients who were ex-smokers (p=0.777, chi-square).

Table 34e

Smoke status	HGD/AC	Non HGD/AC
Current	29	235
Ex	27	237

P=0.777 (chi-square)

There were no significant differences between people who smoked 20 or more a day and those who were current smokers but smoked less than 20 a day and proportions of HGD/AC to non HGD/AC (p=0.577, chi-square) (OR 0.80).
Proportions of HGD/AC to non-HGD/AC were still significantly higher in patients who had given up smoking for less than 10 years compared to those who had never smoked (p=0.046, chi-square) (OR = 2.17) and this remained significant for patients who had given up more than 10 years ago compared to those who had never smoked (p=0.001, chi-square) (OR = 3.24).
The odds ratio for current smokers 20 a day or more vs non-smokers was 2.73; (p=0.004, chi-square) and for current smokers less than 20 a day vs non-smokers, 3.42; (p=0.001, chi-square).
Analyses were repeated dividing the cohort into males and females:
In females, there were no significant differences in proportions of HGD/AC to non-HGD/AC when all smoking categories examined (p=0.687, chi-square).
When divided into those that had ever smoked and those that had never smoked there remained no significant differences (p=0.214); although there did appear to be a trend towards more dysplastic disease in the smoking group (OR 1.75).

Table 35a Smoking status and proportions of dysplastic disease; females

Smoke status	HGD/AC	Non HGD/AC
Ever smoked	12	148
Never smoked	9	194

P=0.214, OR 1.75

There remained no significant differences in proportions of HGD/AC:non HGD/AC when all other smoking categories were examined [Current vs ex-smokers, p=0.610; 20/day vs <20/day, p=0.743;Ex <10 years vs never, p=0.849; Ex >10 years vs never, p=0.391; Current 20/7 vs never, p=0.413 (p=0.314 Fishers) (OR 1.75); Current <20/7 vs never, p=0.180 (p=0.165 Fishers exact) (OR 2.27)]

In males, however, there were significant differences in proportions of HGD/AC to non HGD/AC when all smoking categories examined (p=0.012, chi-square) and the results remained significant when ex-smokers were compared to non-smokers as above (p<0.001, chi-square; OR 3.50).

Table 35b Smoking status and proportions of dysplastic disease; males

Smoke status	HGD/AC	Non HGD/AC
Ever smoked	44	324
Never smoked	9	232

P<0.001 (chi-square), OR 3.50

There were no significant differences in proportions of HGD/AC to non HGD/AC between those who smoked 20 a day and those who smoked less than 20 a day (p=0.534, chi-square) or in current versus ex-smokers (p=0.039, chi-square). There were significantly higher proportions of HGD/AC compared to non-HGD/AC when *all* categories of smoking were compared to those who had never smoked (Ex <10 years vs never p=0.029, OR 2.80; Ex >10 years vs never, p=0.001, OR 4.14; Current 20/7 vs never, p=0.006, OR 3.33; Current <20/7 vs never, p=0.001, OR 4.46)

Logistic regression analysis

Analysis was repeated using logistic regression (binary).

Males and females combined:

There was a significant relationship between smoking ('ever' smoked) and the risk of developing HGD/AC compared to those that had never smoked; p<0.001, OR=2.81; this was true for ex-smokers (>10years) compared with never smoked p=0.001, OR=3.24, current (<20) vs never smoked p=0.002, OR=2.71 and current (>20) vs never smoked p=0.006, OR =2.73; but interestingly did not quite reach significance for ex-smokers (<10 years) vs never smoked p=0.051, OR=2.17.

Data were analysed separately for males and females and the results presented in Table 36:

Table 36 Summary of output of logistic regression analysis on risk of development of HGD/AC and smoking status; males and females analysed separately

	Males		Females	
	P value	OR	P value	OR
Never vs ever	0.001	3.50	0.219	1.75
Never vs ex>10yrs	0.002	4.14	0.397	1.80
Never vs ex<10yrs	0.035	2.80	0.849	1.17
Never vs current<20	0.003	4.46	0.191	2.30
Never vs current≥20	0.009	3.33	0.419	1.75

Alcohol

915 (71.4%) of patients had documentation of frequency of alcohol usage in the notes.

When patients are grouped by worst disease diagnosed the following table of alcohol consumption is produced:

Table 37a Alcohol score and grade of disease

	Alcohol score				
Diagnosis	1	2	3	4	Total
CLO (visual)	73	10	3	12	98
CLO (histo)	101	13	11	13	138
CLO (IM)	227	51	26	28	332
CLO (ID)	13	6	3	1	23
CLO (ID+IM)	64	11	10	10	95
LGD	110	30	13	9	162
HGD	11	2	1	3	17
AC	38	4	4	4	50
Total	637	127	71	80	915

There were no significant differences in frequency of alcohol score and disease at worst diagnosis (p=0.384; chi square). On regrouping disease into non HGD/AC vs HGD/AC (see Table 37b) there remained no significant differences in frequency of alcohol score and proportions of disease (p=0.650, chi-square).

Table 37b

	Alcohol score				
Diagnosis	1	2	3	4	Total
Non HGD/AC	588	121	66	73	848
HGD/AC	49	6	5	7	67
Total	637	127	71	80	915

P=0.650 (chi-square)

On re-grouping alcohol consumption by gender (see Tables 38a and b) there remained no significant differences in frequency of alcohol score and disease subtypes overall, or for HGD/AC vs non HGD/AC (males: p=0.277 and p=0.639, chi-square) (females: p=0.412 and p=0.523, chi-square).

Table 38a Alcohol score and grade of disease; females only

	Alcohol score				
Diagnosis	1	2	3	4	Total
Non HGD/AC	278	19	9	9	315
HGD/AC	17	0	0	0	17
Total	295	19	9	9	332

P=0.523 (chi square)

Table 38b Alcohol score and grade of disease; males only

	Alcohol score				
Diagnosis	1	2	3	4	Total
Non HGD/AC	310	102	57	64	533
HGD/AC	32	6	5	7	50
Total	342	108	62	71	583

P=0.639 (chi square)

On further chi-square analyses done after re-grouping alcohol score into 1 (1-2) and 2 (3-4) (see Table 11b, methods) - firstly, comparing proportions of all disease subtypes[†] and then HGD/AC vs non HGD/AC[‡] - there remained no significant differences for males and females combined or when examined separately (combined; p=0.860[†] and 0.747[‡]) (males; p=0.578[†] and 0.834[‡]) (females; p=0.259[†] and 0.311[‡])

Co-morbidity

Frequencies of associated specific co-morbidities were examined in patients with CLO (all grades of disease) and are presented in the table below:

Table 40a Frequency (as percentages) of associated co-morbidity:

Orthopaedic/rheumatological	18.3	Cerebral vascular disease	6.6
Gastrointestinal disease	6.1	Arrhythmias	5.3
Genitourinary disease	4.2	Hypertension	15.0
Thyroid disease	2.4	Diabetes	4.0
Respiratory disease	2.1	Fibroids	0.2
Cardiovascular disease	2.4	Neurological	10.3
Ischaemic heart disease	14.4	Haematological	2.5
Congestive cardiac failure	4.4	Peripheral vascular disease	3.4

malignancy		***surgery***	
Breast cancer	1.6	cholecystectomy	4.0
Stomach cancer	0.2	antireflux	2.9
Colorec cancer	1.2	hysterectomy	3.6
Prostate cancer	1.2		
Thyroid cancer	0.0		
Lung cancer	0.5		

Proportions of HGD/AC vs non HGD/AC were analysed in patients with and without specific co-morbidities and results are summarised in table 40b. On chi-square analysis, specific co-morbidities were not significantly associated with increased proportions of HGD/AC except in patients with fibroid disease ($p=0.014$, Fishers exact). P values for the chi-square analysis are presented in Table 40c.

Table 40b Associated co-morbidity and proportions of HGD/AC

Associated Co-morbidity	Non HGD/AC (n=1186)		HGD/AC (n=91)	
	yes	**no**	**yes**	**no**
Ortho/rheum	220	966	13	78
GI	71	1115	7	84
GU	50	1136	3	88
Thyroid	30	1156	1	90
Respiratory	25	1161	2	89
CVS	29	1157	2	89
IHD	172	1014	12	79
CCF	53	1133	3	88
PVD	42	1144	2	89
CVA/TIA	77	1109	7	84
Arrhythmias	65	1121	3	88
HT	174	1012	18	73
DM	49	1137	2	89
Cholecystectomy	47	1139	4	87
Fundoplication	35	1151	2	89
Breast ca	21	1165	0	91
Stomach ca	2	1184	1	90
Colorectal ca	14	1172	1	90
Prostate ca	13	1173	2	89
Lung ca	7	1179	0	91
Fibroids	1	1185	2	89
Hysterectomy	42	1144	4	87
Neurological	119	1067	12	79
Haematological	29	1157	3	88

Table 40c P values for chi-square analysis of data: Table 40b

Ortho/rheum	0.310	CVA/TIA	0.656	Prostate ca	0.347
gastro	0.513	Arrhyth	0.371	Lung ca	0.462
GU	0.672	HT	0.189	fibroids	0.000*
thyroid	0.393	DM	0.364	hyst	0.673
resp	0.954	Chole	0.839	neuro	0.339
cardio	0.883	Fundop	0.680	haem	0.616
IHD	0.731	Breast ca	0.201		
CCF	0.599	Stomach ca	0.077		
PVD	0.498	Colorec ca	0.945		

* Fishers exact p=0.014

Diagnosis of CLO

The total number of patients diagnosed with CLO over the time bands is presented in Figure 13.

Distribution of disease at diagnostic OGD

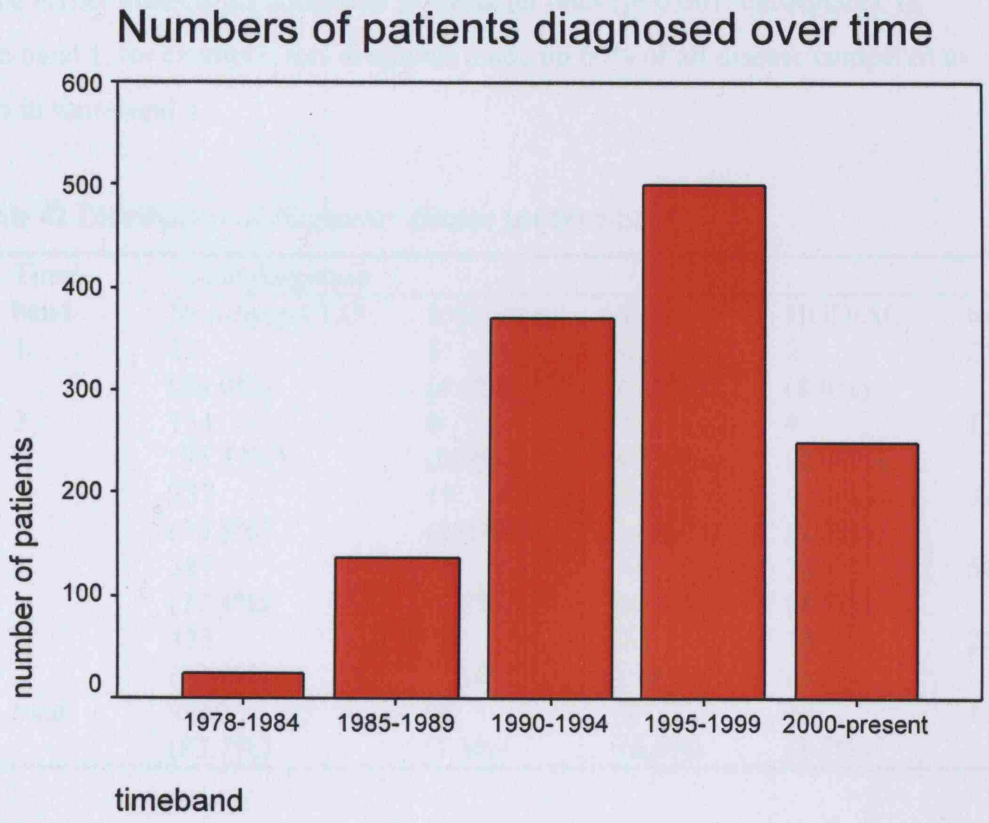
The table below shows the distribution of disease at first diagnostic OGD.

Table 41 Distribution of disease at initial diagnosis

Disease at diagnosis	Number of patients	Percentage
CLO (visual)	407	31.7
CLO (histo)	229	17.9
CLO (IM)	424	33.1
CLO (ID)	28	2.2
CLO (ID+IM)	66	5.2
Low Grade Dysplasia	83	6.5
High Grade Dysplasia	14	1.1
Adenocarcinoma	31	2.4
Total	1282	100.0

407 (31.7%) patients were diagnosed as having CLO at endoscopy without histological confirmation of CLO on that occasion. Of these, 261 (64.1%) went on to have subsequent histological confirmation of a diagnosis of CLO (histo) or worse at a later stage. 81 (19.9%) progressed to dysplasia/AC (diagnoses 6-8).
23 (5.7%) had biopsies taken at diagnosis that were negative for CLO (either just showing squamous epithelium or inflammatory cells). Of these 16 (69.6%) went on to have biopsy proven CLO at a later date.
229 (17.9%) patients were diagnosed with CLO on histology but no documentation of associated IM present (diag 2). Of these 65 (28.4%) developed worsening histology (diag 3 or >). 23 (10.2%) developed dysplasia/AC – 19 LGD, 1 HGD and 3 ACs.
The total number of patients with CLO but no evidence of IM (diag 1 and 2) was 635; which is 49.5% of the entire cohort. Of these, 330 (52.0%) went on to progress to a more severe histological diagnosis, with 104 (16.4%) developing a diagnosis of dysplasia/AC.

Figure 13 *Numbers of patients diagnosed with CLO (all grades of disease) over the time-bands



* Last column represents 2000-2004. The registry was set up in 1996 which may partially explain the peak in patients diagnosed (and registered) over this time-band.

Proportions of grades of disease diagnosed over the 5 time-bands varied (see Figures 14a-e).

There is a trend for a more frequent diagnosis of non-histologically proven CLO in the earlier time-bands compared to the latter ones ($p<0.001$, chi-square). In time-band 1, for example, this diagnosis made up 60% of all disease compared to 11% in time-band 5.

Table 42 Distribution of diagnostic disease per time-band

Time-band	Initial diagnosis				
	Non-dysp CLO	Indef dysp	LGD	HGD/AC	total
1	22 (88.0%)	1 (4.0%)	0 (0.0%)	2 (8.0%)	25
2	131 (96.32%)	0 (0.0%)	1 (0.74%)	4 (2.94%)	136
3	337 (90.8%)	15 (4.07%)	15 (4.07%)	4 (1.08%)	371
4	387 (77.4%)	48 (9.6%)	43 (8.6%)	22 (4.4%)	500
5	183 (73.2%)	30 (12.0%)	24 (9.6%)	13 (5.2%)	250
total	1060 (82.7%)	94 (7.3%)	83 (6.5%)	45 (3.5%)	1282

Figure 14 a-e Pie charts to show distribution of disease diagnosed over time-bands

Figure 14a

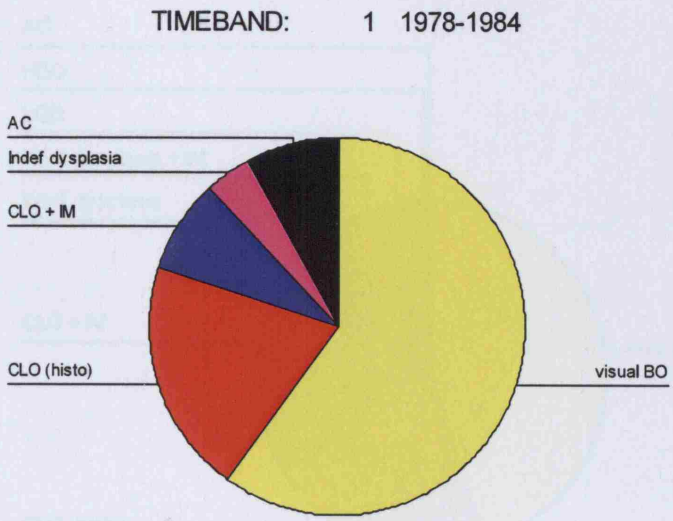


Figure 14b

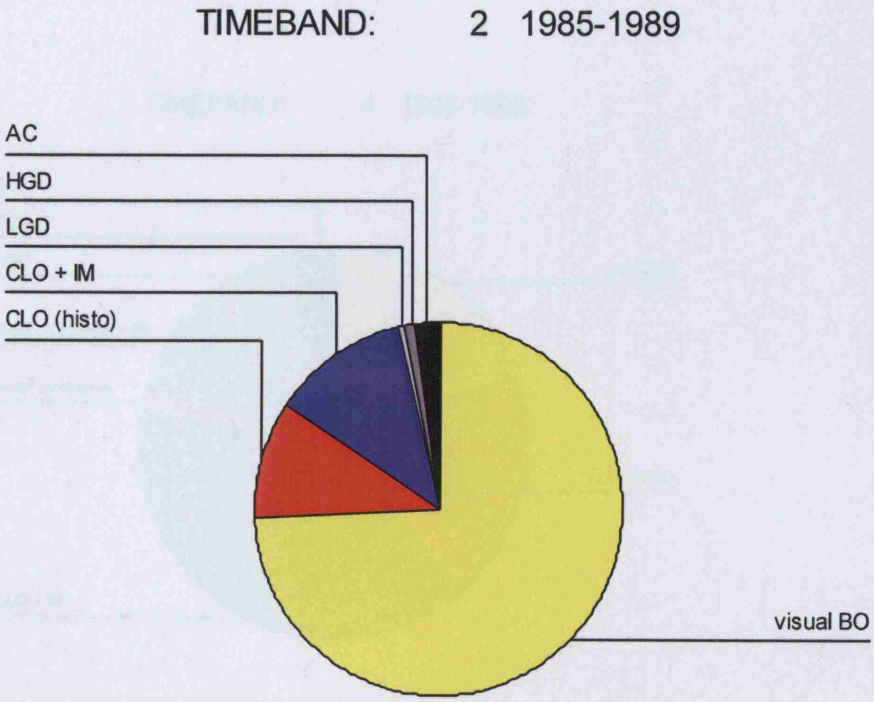


Figure 14c

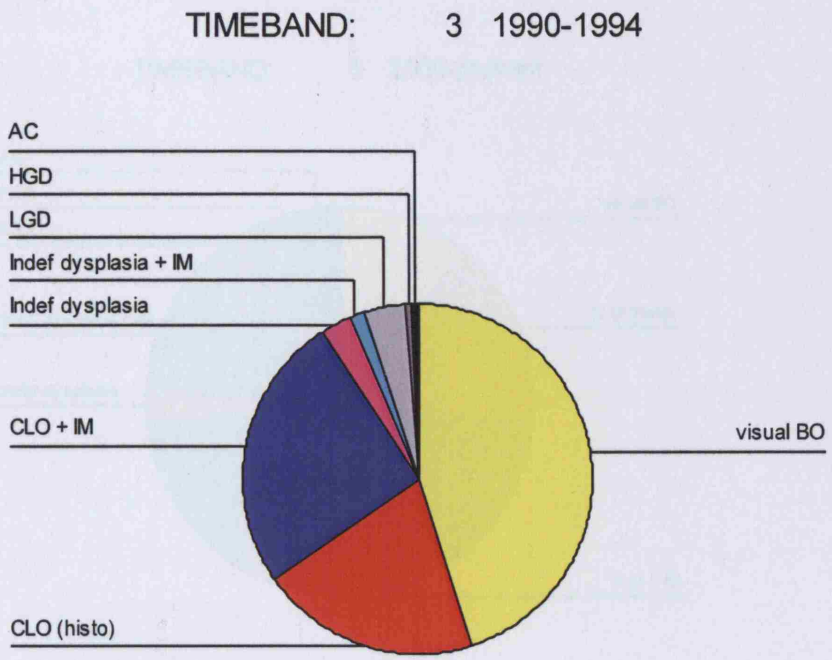


Figure 14c

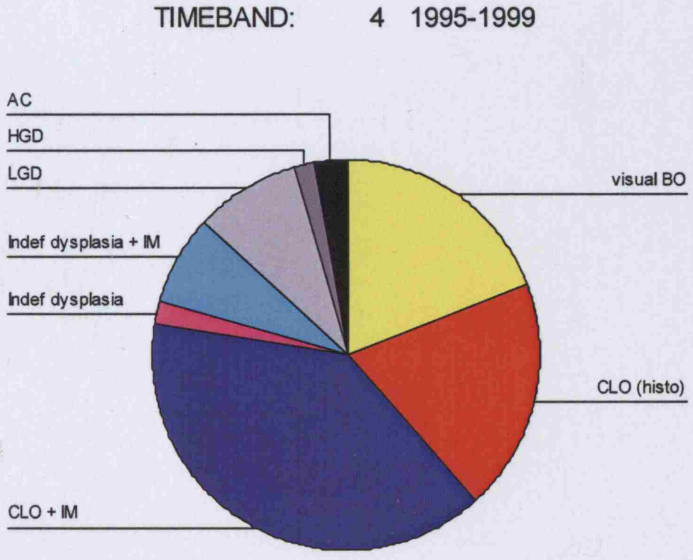
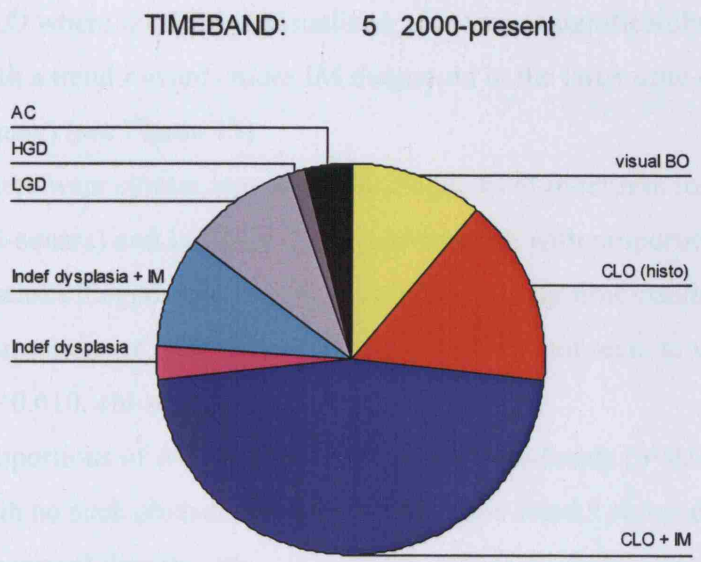


Figure 14d


TIMEBAND: 5 2000-present
AC
HGD
LGD
Indef dysplasia + IM
Indef dysplasia
visual BO
CLO (histo)
CLO + IM

On further analysis examining the diagnosis of uncomplicated CLO alone, proportions of CLO diagnosed with the associated presence of IM compared with CLO where no IM was visualized, also varied significantly across the time-bands with a trend towards more IM diagnosed in the latter time-bands ($p=0.001$; chi-square) (see Figure 15).

There were similar trends for the diagnosis of indefinite for dysplasia ($p<0.001$, chi-square) and LGD ($p<0.001$, chi-square), with proportions of both of these diseases diagnosed more frequently in the latter time-bands. (see Figures 16,17)

Proportions of HGD diagnosed over time did not seem to vary significantly ($p=0.610$, chi-square).

Proportions of AC did vary between the time-bands ($p=0.019$, chi-square) but with no such obvious trend over time (time-band 3 showed significantly less AC diagnosed than the other time-bands; $p=0.005$, chi-square).

Figure 15 Diagnosis of CLO + IM over time

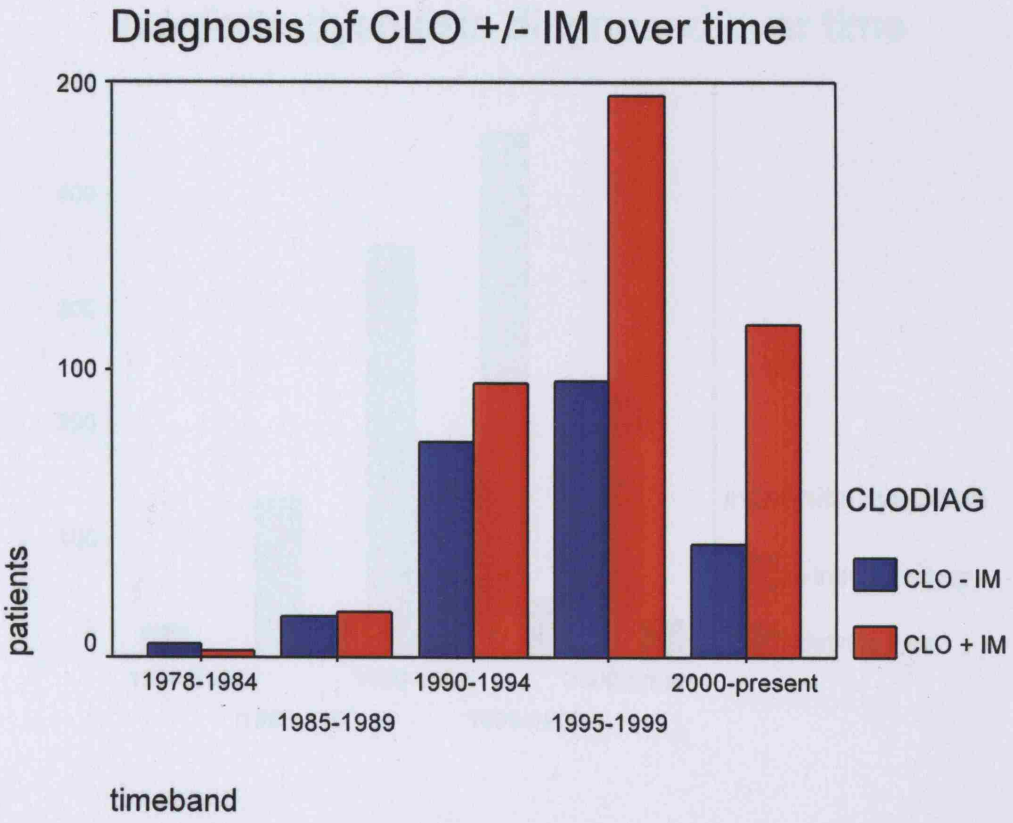


Figure 16 Diagnosis of indefinite for dysplasia over time

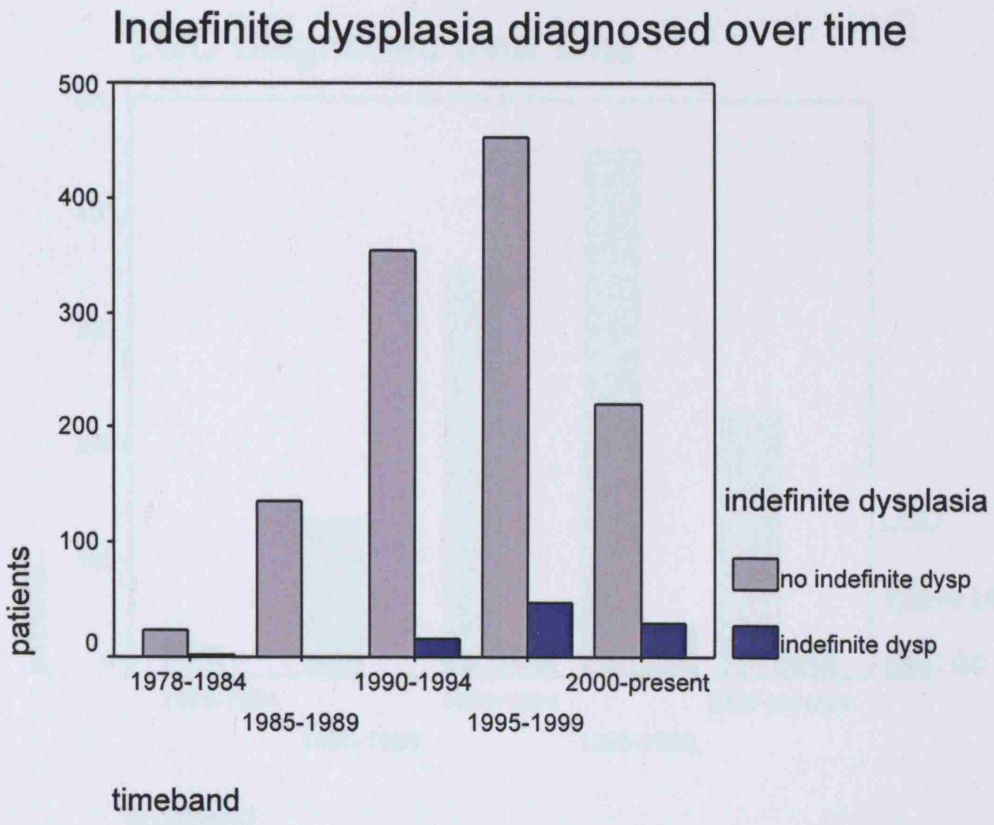
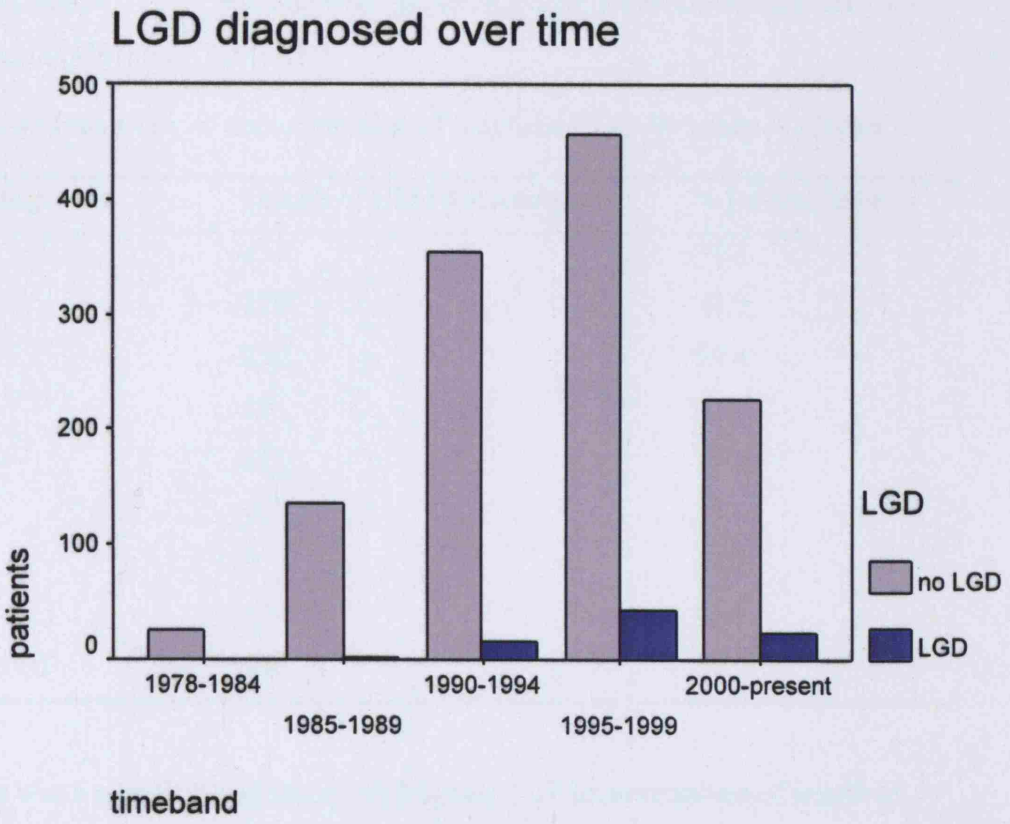


Figure 17 Diagnosis of LGD over time



Length Of columnarised segment

746 patients (58.2% of the total) had a length of CLO documented in the notes. Frequency of documentation of length varied depending on the diagnosis and ranged from 41.9% of patients with AC to 78.8% of patients with indefinite for dysplasia (+IM) (see Table 43).

Table 43 Frequency of documentation of length of CLO per grade of disease

Diagnosis	Length of CLO documented	% (of that diag)
1	233	57.3
2	122	53.3
3	252	59.4
4	19	67.9
5	52	78.8
6	46	55.4
7	9	64.3
8	13	41.9
Total	746	58.2

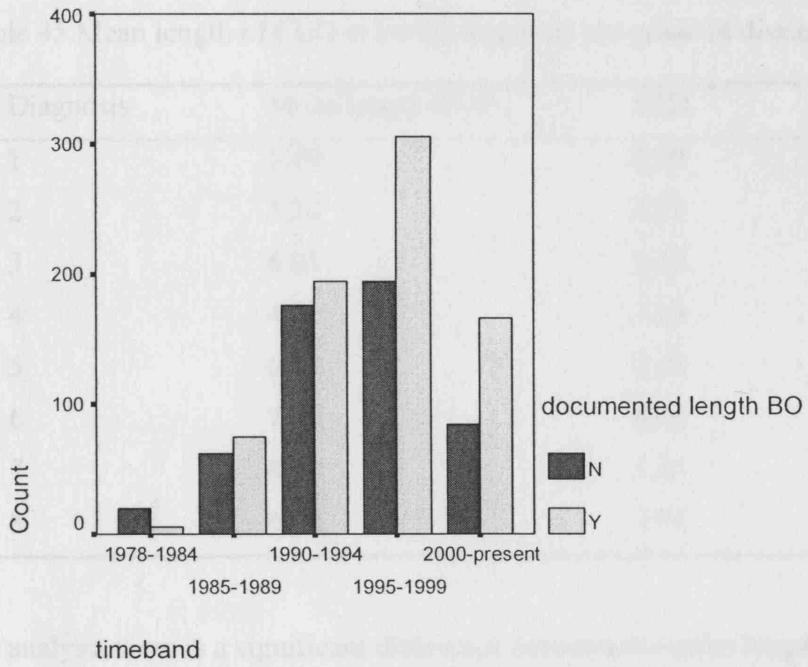
There was a significant difference in frequency of documentation of length of CLO segment over the time-bands with the latter time-bands recording a much higher proportion of lengths ($p<0.001$, chi-square) (Table 44) (see Figure 18).

Table 44 Documentation of length of CLO over the time-bands

		Documentation of length CLO	
Time band		yes	no
	Time 1	5 (20.0%)	20 (80.0%)
	Time 2	74 (54.4%)	62 (45.6%)
	Time 3	195 (52.6%)	176 (47.4%)
	Time 4	306 (61.2%)	194 (38.8%)
	Time 5	166 (66.4%)	84 (33.6%)

P<0.001 (chi-square)

Figure 18 Frequency of documentation of length of CLO at diagnosis over time



The mean lengths of CLO recorded per initial diagnosis vary and are presented in the table below (see Figure 19):

Table 45 Mean length of CLO at initial diagnosis per grade of disease

Diagnosis	Mean length CLO	STD	SE mean
1	5.49	3.70	0.24
2	5.30	3.51	0.32
3	6.03	3.40	0.21
4	4.55	2.84	0.65
5	6.18	3.40	0.47
6	7.52	4.42	0.65
7	8.78	3.35	1.12
8	6.08	3.81	1.06

On analysis there is a significant difference between the mean lengths of CLO recorded per initial diagnosis ($p=0.001$, one way anova) with patients with LGD and HGD having significantly longer lengths of CLO than patients with less severe disease ($p=0.001$; $p=0.014$; Indep T). However, in patients with AC the length of CLO recorded seems to be shorter than HGD or LGD.

When patients with HGD and AC are grouped together and compared with non-HGD/AC there is no significant difference between length of CLO observed ($p=0.078$).

When the diagnostic categories are reorganised into non-dysplastic CLO, Indefinite for dysplasia, LGD and HGD/AC (see Table 46) there are still significant differences in mean lengths of CLO observed ($p=0.002$).

Figure 19 Mean lengths of CLO per grade of disease diagnosed

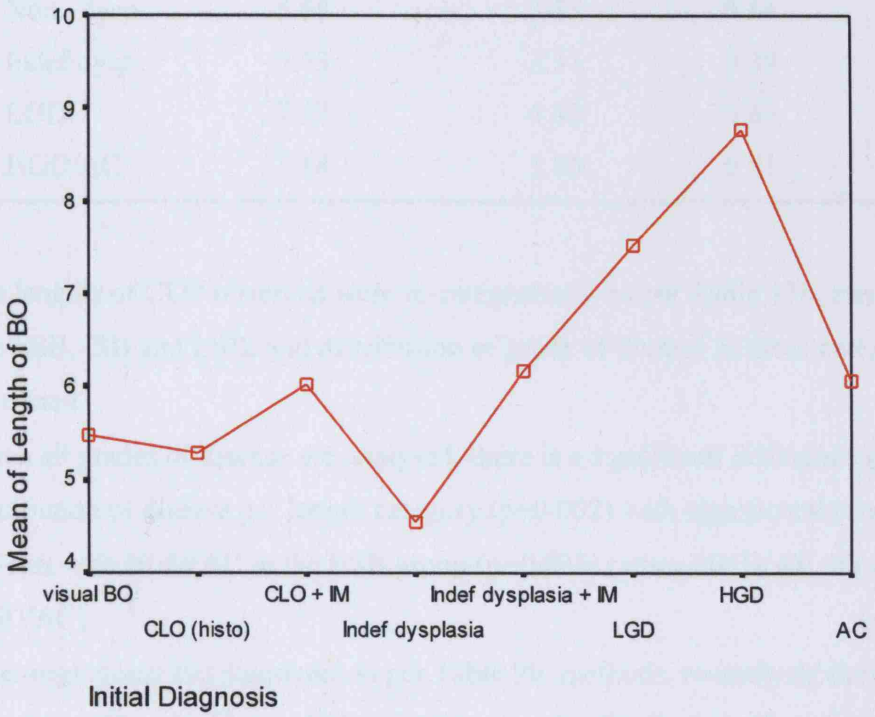


Table 46 Mean length of CLO at initial diagnosis (disease regrouped)

Diagnosis	Mean length CLO	STD	SE mean
Non –dysp	5.68	3.55	0.14
Indef dysp	5.75	3.31	0.39
LGD	7.52	4.42	0.65
HGD/AC	7.18	3.80	0.81

The lengths of CLO observed were re-categorised - as per Table 13b, methods - into SSB, ISB and LSB, and distribution of grade of disease in these categories examined.

When all grades of disease are analysed, there is a significant difference in distribution of disease per length category (p=0.002) with significantly more patients with HGD/AC in the LSB group (p=0.035) (when HGD/AC cf non-HGD/AC).

After regrouping the diagnoses as per Table 9b, methods, re-analysis showed there was still a significant difference between the distribution of grade of disease in each of the length categories (p=0.013) (see Table 47), with 59.1% of patients with HGD/AC having long segment Barrett's compared to 31.4% of patients with non-dysplastic disease.

Table 47 Mean length of CLO regrouped per diagnostic disease

Diagnosis	Length of CLO category			
	SSB	ISB	LSB	Total
Non-dysp CLO	190 (31.4%)	226 (37.3%)	190 (31.4%)	606
Indef dysp	24 (33.8%)	20 (28.2%)	27 (38.0%)	71
LGD	7 (15.2%)	17 (37.0%)	22 (47.8%)	46
HGD/AC	5 (22.7%)	4 (18.2%)	13 (59.1%)	22
Total	226 (30.3%)	267 (35.8%)	252 (33.8%)	745

P=0.013 (chi-square)

The mean length of CLO documented for all disease subtypes in each of the 5 time-bands ranged from 4.78cm to 6.24cm with no significant differences between them (p=0.054, one-way anova).

Table 48 Mean length of CLO diagnosed per time-band

Time-band	Mean length CLO (cm)	STD	SE mean
1	5.40	2.70	1.21
2	4.78	2.82	0.33
3	6.24	3.87	0.27
4	5.93	3.68	0.21
5	5.67	3.48	0.27

P=0.054 (one-way anova)

When segment lengths were reclassified into short (SSB) (3cm or less) vs long (LSB) (anything >3cm) there were still no differences in frequency of diagnosis overall over the various time-bands (p=0.134). Time-band 3, however, did have statistically lower proportions of SSB diagnosed when compared separately to all other time-bands (p=0.025, chi-square).

Presence of non-confluent disease

The overall frequency of associated non-confluent disease per diagnosis is presented in Table 49.

Table 49 Presence of associated non-confluent disease per grade of disease at initial diagnosis

Initial diagnosis:	Presence of non-confluent disease		Total
	Yes	No	
CLO (visual)	43 (10.6%)	364 (89.4%)	407
CLO (histo)	14 (6.1%)	215 (93.9%)	229
CLO (IM)	17 (4.0%)	407 (96%)	424
CLO (ID)	4 (14.3%)	24 (85.7%)	28
CLO (ID+IM)	5 (7.6%)	61 (92.4%)	66
LGD	10 (12.0%)	73 (88.0%)	83
HGD	0 (0%)	14 (100%)	14
AC	1 (3.2%)	30 (96.8%)	31
All grades	94 (7.3%)	1188 (92.7%)	1282

Overall, documentation of associated non-confluent disease was infrequent, ranging from 0% of HGD to 14.3% of indefinite for dysplasia (no IM) (see Figure 20).

However, on analysis, there is a significant difference in proportion of non-confluent disease per grade of disease diagnosed with a trend toward more dysplastic disease being associated with *less* non-confluent disease (ie more circumferential) ($p=0.009$, chi-square).

The presence of non-confluent disease per diagnosis was re-analysed with segment length groups re-categorised into short, intermediate and long.

There were significant differences in proportions of non-confluent:confluent disease diagnosed per grade of histology for patients with short segment CLO ($p=0.010$), with patients with more severe histology appearing to have less non-confluent disease (ie. more likely to have circumferential disease only).

This was also the case for intermediate segment disease ($p=0.008$) but *not* the case for long segment disease ($p=0.586$).

There was a significant difference in the frequency of diagnosis of non-confluent disease over the time-bands ($p<0.001$); with significantly less non-confluent disease being diagnosed in time-band 5 ($p=0.002$) and significantly more in time-band 2 ($p<0.001$) when analysed separately (see Table 50) (see Figure 21)

Figure 20 Proportion of non-confluent documented per grade of disease diagnosed

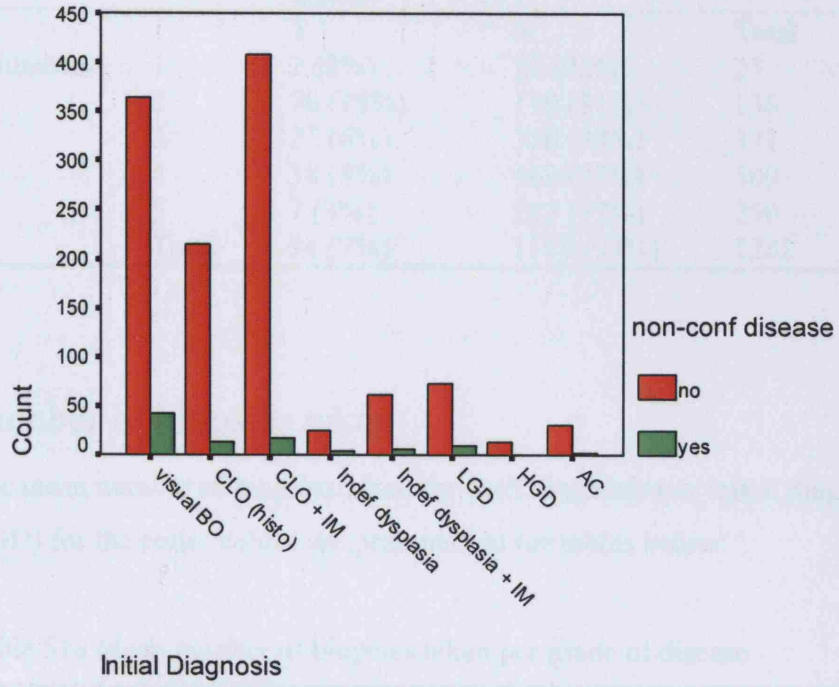


Figure 21 Proportion of non-confluent disease diagnosed over time

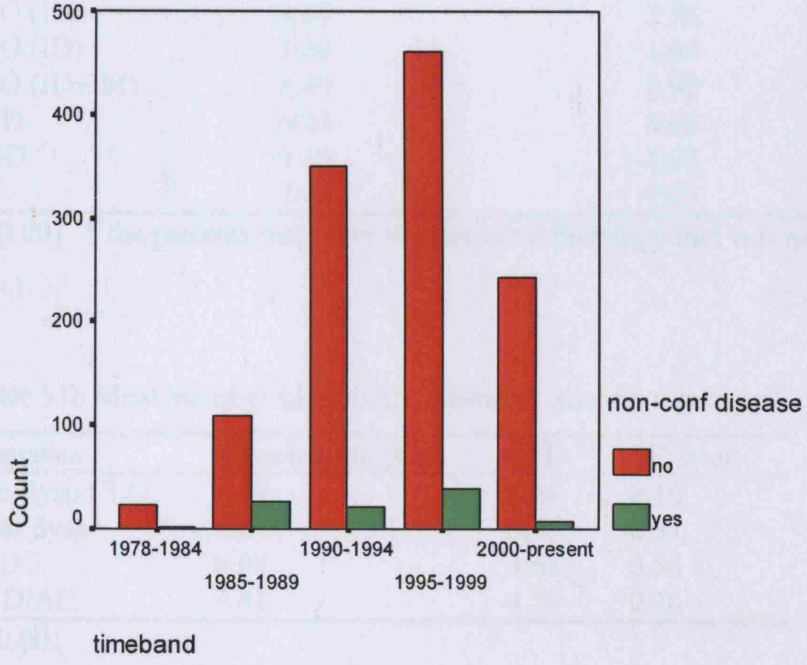


Table 50 Diagnosis of non-confluent disease over time:

		Presence of non-confluent disease		
		Y	N	Total
Timeband	1	2 (8%)	23 (92%)	25
	2	26 (19%)	110 (81%)	136
	3	21 (6%)	350 (94%)	371
	4	38 (8%)	462 (92%)	500
	5	7 (3%)	243 (97%)	250
	Total	94 (7%)	1188 (93%)	1282

Number of biopsies taken

The mean number of biopsies taken for each diagnosis (on initial diagnostic OGD) for the entire cohort are presented in the tables below:

Table 51a Mean number of biopsies taken per grade of disease

Diagnosis	Mean no. biopsies	STD	SE mean
CLO (visual)*	5.16	4.87	1.11
CLO (histo)	4.30	4.01	0.30
CLO (IM)	4.69	3.76	0.19
CLO (ID)	3.60	1.04	0.21
CLO (ID+IM)	5.40	3.92	0.49
LGD	6.03	4.68	0.54
HGD	8.10	4.95	1.57
AC	7.09	4.03	0.86

$P<0.001$ * the patients that were biopsied had histology that was *negative* for CLO

Table 51b Mean number of biopsies taken per disease, regrouped

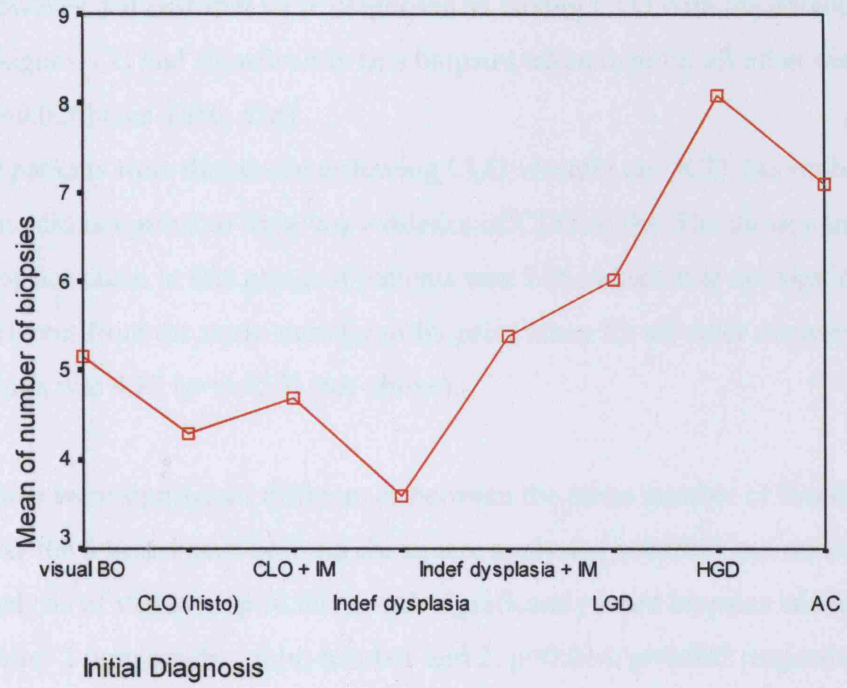
Diagnosis	Mean no. biopsies	STD	SE mean
Non-dysp CLO	4.59	3.88	0.16
Indef dysp	4.89	3.45	0.37
LGD	6.03	4.68	0.54
HGD/AC	7.41	4.29	0.76

$P<0.001$

On analysis, there are significant differences between the mean number of biopsies taken per diagnosis with significantly more biopsies taken for the diagnosis of more dysplastic disease ($p<0.001$, one-way anova) (see Figure 22). On separate analysis examining mean number of biopsies taken for specific grades of disease compared to mean biopsy number taken for all other diagnoses, patients with LGD, HGD and AC all had significantly more biopsies taken ($p=0.008$, 0.010, <0.001 respectively, one-way anova). These differences remained true when re-analysing the data grouping patients into numbers of biopsies taken – ie, 0-3, 3-6, 6-10 and 10+ - and examining categorical data using Pearson chi-square.

The mean number of biopsies taken for the diagnosis of *non*-HGD/AC were 4.77 (STD: 3.94; SE mean: 0.14) and for HGD/AC were 7.41 which were significantly different on independent T-Test analysis ($p<0.001$).

Figure 22 Mean number of biopsies taken for the diagnosis of each grade of disease



Biopsy number and diagnosis of IM

The mean number of biopsies taken when diagnosing CLO without evidence of IM was 4.30, and for CLO with IM; 4.69, with no statistically significant difference between the two on independent T-Test analysis (p=0.252). However, patients that were diagnosed as having CLO with the absence of IM (diagnosis 2) had significantly less biopsies taken than for all other diagnoses (p=0.026) (see Table 51a).

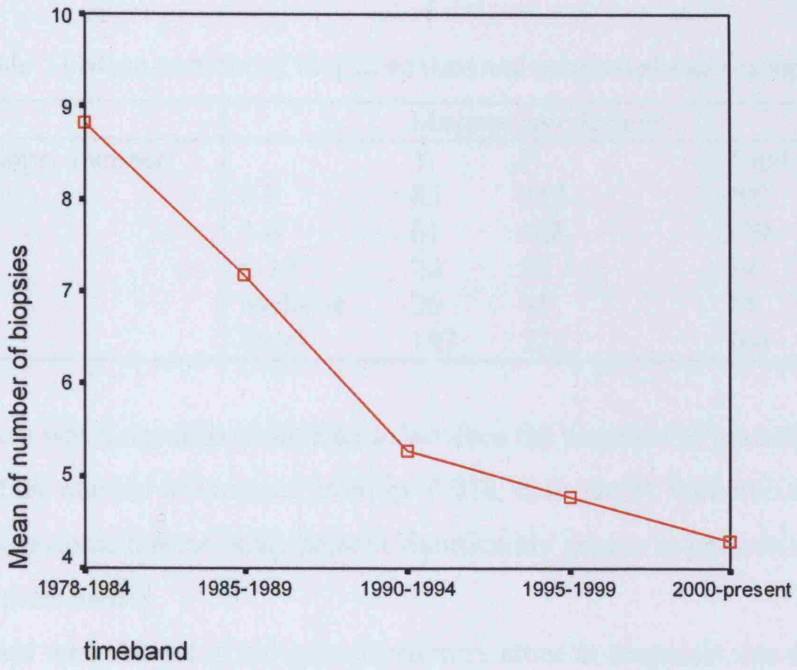
19 patients were diagnosed as having CLO visually on OGD, but on biopsy at that time did not prove to have any evidence of CLO or IM. The mean number of biopsies taken in this group of patients was 5.16, which was not significantly different from the mean number of biopsies taken for all other diagnoses (2-8) which was 4.87 (p=0.755) (see above).

There were significant differences between the mean number of biopsies taken over the 5 time-bands both on chi square analysis (p<0.001) and on one-way analysis of variance (p<0.001), with significantly more biopsies taken in the earlier 2 time-bands – time-bands 1 and 2; p=0.014; p=0.002 respectively (see Table 52, see Figure 23). There were significantly less biopsies taken in time-band 5 vs others (p=0.013).

Table 52 Mean number of biopsies taken over the 5 time-bands

Timeband	Mean no. biopsies	STD	SE mean
1	8.83	6.77	2.76
2	7.18	5.98	1.13
3	5.26	4.48	0.34
4	4.78	3.73	0.20
5	4.29	3.32	0.23

Figure 23 Mean number of biopsies taken (all grades of disease) over time



Macrosopic lesions at diagnosis – and biopsy number

The presence of oesophageal macrosopic lesions and the association with numbers of biopsies taken is presented in the table below:

Table 53 Mean number of biopsies taken and associated macroscopic lesions

	Macroscopic lesions		
Biopsy number	Y	N	Total
0-3	85	317	402
3-6	61	168	229
6-10	20	39	59
Multiple	26	48	74
Total	192	572	764

There was a significant correlation between the presence of macroscopic lesions and the number of biopsies taken (p=0.018, chi-square), with the chances of macroscopic lesions being present significantly greater in patients that had more biopsies taken.

When the presence of associated strictures alone at diagnosis was examined (Table 54) there appeared to be trend towards them being more common in patients undergoing more biopsies, however this did not reach statistical significance (p=0.056).

Table 54 Mean number of biopsies taken and associated oesophageal strictures

	Stricture		
Biopsy number	Y	N	Total
0-3	21	381	402
3-6	16	213	229
6-10	8	51	59
Multiple	8	66	74
Total	53	711	764

When the association of ulcers at diagnosis was examined there was a significant association with the number of biopsies taken, with patients with ulcers more likely to have undergone a greater number of biopsies (p=0.011).

Macroscopic lesions and grade of disease diagnosed

The numbers of patients with evidence of macroscopic disease (ulcers. strictures or any other oesophageal lesion) at diagnosis and the grade of dysplasia subsequently diagnosed is presented in the table below:

Table 55 Grade of disease diagnosed and associated macroscopic lesions

		Macroscopic lesions at diagnosis		
		Y	N	Total
Diagnosis	LGD	28 (33.7%)	55 (66.3%)	83
	HGD	8 (57.1%)	6 (42.9%)	14
	AC	27 (87.1%)	4 (12.9%)	31

When proportions of macroscopic disease for patients with a diagnosis of LGD, HGD and AC were compared with all other disease there were significantly more macroscopic lesions present in the dysplastic disease groups ($p=0.008$, $p=0.001$, $p<0.001$, respectively) with frequency of macroscopic disease at diagnosis increasing with severity of dysplasia.

Macroscopic lesions over time

There was a significant difference in the frequency of diagnosis of ulcers over the time-bands ($p<0.001$, chi-square) with a higher proportion of ulcers diagnosed in time-band 5 ($p<0.001$). However, there was no significant difference in the frequency in diagnosis of strictures over time ($p=0.212$, chi-square).

4 Quadrant biopsy technique

The documented use of biopsies taken using a '4 quadrant technique' in each time-band was rare and ranged from 0% to 12.4% of all biopsies taken.

The most frequently documented use of this technique appeared in time-band 4, and was only really documented at all in the latter 2 time-bands, with a significant difference seen when all 5 time-bands were compared ($p<0.001$).

The frequency of documented use of a 4 quadrant biopsy technique ranged from 0.2% of all biopsies for CLO (visual)* to 21.2% for indefinite dysplasia (+IM).

* biopsies taken in the presence of CLO (visual) with *non-confirmatory* histology

There was a significant difference between the grades of disease being diagnosed and the documented frequency of use of the 4 quadrant biopsy technique ($p<0.001$; chi-square) (Table 56a).

When proportions of non dysplastic (diag 1-5) to dysplastic (6-8) disease are examined there appeared to be a significant difference in frequency of use of a 4 quadrant technique with significantly higher proportions of dysplastic disease (12.5% as opposed to 4.9% of non-dysp disease) diagnosed on 4 quadrant biopsy ($p<0.001$, chi-square) (Table 56b).

However, when disease is grouped into non HGD/AC and HGD/AC these differences are no longer observed ($p=0.333$, chi-square) (Table 56c).

Table 56a Grade of disease diagnosed and frequency of 4 quadrant biopsies

		4 quadrant biopsy		*Total*
		N	Y	
Initial Diagnosis	visual BO	406 (99.8%)	1 (0.2%)	407
	CLO (histo)	222 (96.9%)	7 (3.1%)	229
	CLO + IM	392 (92.5%)	32 (7.5%)	424
	Indef dysplasia	26 (92.9%)	2 (7.1%)	28
	Indef dysplasia + IM	52 (78.8%)	14 (21.2%)	66
	LGD	71 (85.5%)	12 (14.5%)	83
	HGD	13 (92.9%)	1 (7.1%)	14
	AC	28 (90.3%)	3 (9.7%)	31
Total		1210 (94.4%)	72 (5.6%)	1282

P<0.001 (chi-square)

Table 56b Non-dysplastic vs dysplastic disease and 4 quadrant biopsy

		4 quadrant biopsy		*Total*
		N	Y	
Diagnosis	Non-dysplastic disease	1098 (95.1%)	56 (4.9%)	1154
	dysplastic disease	112 (87.5%)	16 (12.5%)	128
Total		1210 (94.4%)	72 (5.6%)	1282

P<0.001 (chi-square)

Table 56c Non HGD/AC vs HGD/AC and 4 quadrant biopsy technique

		4 quadrant biopsy		*Total*
		N	Y	
Diagnosis	Non-HGD/AC	1169 (94.5%)	68 (5.5%)	1237
	HGD/AC	41 (91.1%)	4 (8.9%)	45
Total		1210 (94.4%)	72 (5.6%)	1282

P=0.333 (chi-square)

Comparison between centres

Distribution of disease between centres

There were significant differences in the proportions of grades of disease diagnosed between the centres (p<0.001, chi-square) (see Figures 24a-e). Proportions of diagnosis of non-histologically proven CLO varied significantly between the centres (p<0.001, chi-square) with centres 2,3 and 4 recording significantly lower proportions (p=0.009, p<0.001 and p<0.001, chi-square, respectively) and centres 5 and 6 significantly more (p<0.001 and p=0.002, chi-square, respectively).

On examination of proportions of CLO+IM : CLO-IM diagnosed between the centres (Table 58) there are significant differences overall (p<0.001, chi-square), with centres 3 and 4 having significantly higher proportions of CLO+IM (p<0.001, chi-square) and centre 6 significantly lower (p<0.001, chi-square).

Table 57 Proportion of CLO +/- IM diagnosed per centre

		CLO - IM	CLO + IM	Total
Centre	1	57 (41.3%)	81 (58.7%)	138
	2	24 (49.0%)	25 (51.0%)	49
	3	14 (15.4%)	77 (84.6%)	91
	4	13 (16.6%)	65 (83.4%)	78
	5	61 (33.2%)	123 (66.8%)	184
	6	60 (53.1%)	53 (46.9%)	113
Total		229 (35.1%)	424 (64.9%)	653

P<0.001 (chi-square)

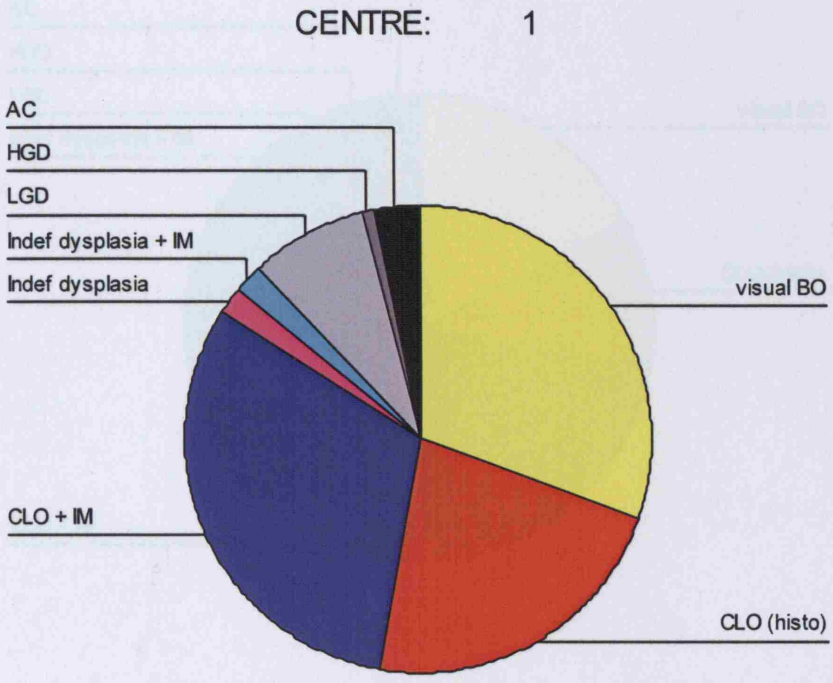
Proportions of disease that were indefinite for dysplasia diagnosed between the centres varied significantly (p<0.001, chi-square); with centre 4 diagnosing

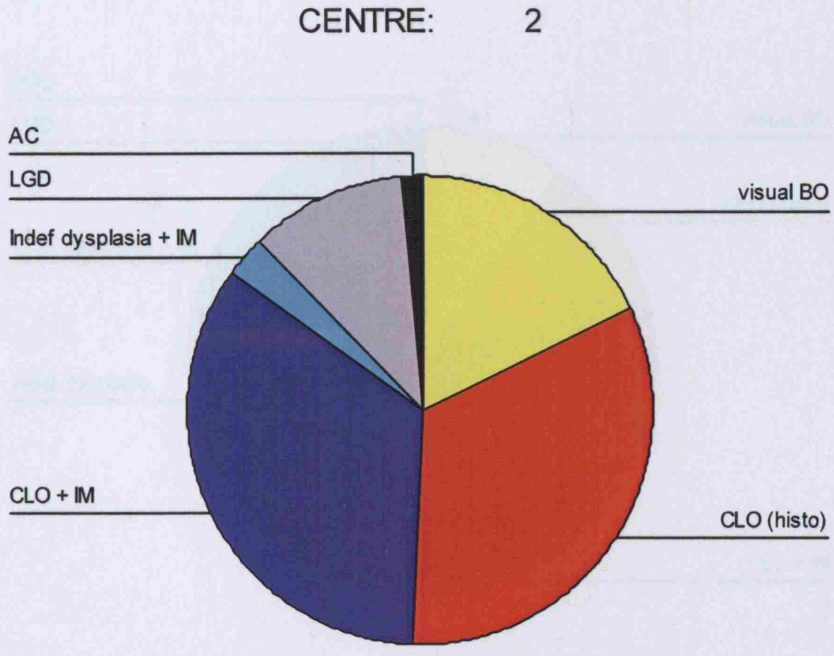
significantly more than the other centres (19.8% of all grades of disease) ($p<0.001$, chi-square) and centre 6 significantly less (1.9% of all grades of disease) ($p=0.001$, chi-square).

On examination of proportions of LGD diagnosed there are significant differences between the centres ($p<0.001$, chi-square) with centres 3 and 6 having particularly low numbers of patients diagnosed ($p=0.035$ and $p<0.001$ respectively, chi-square).

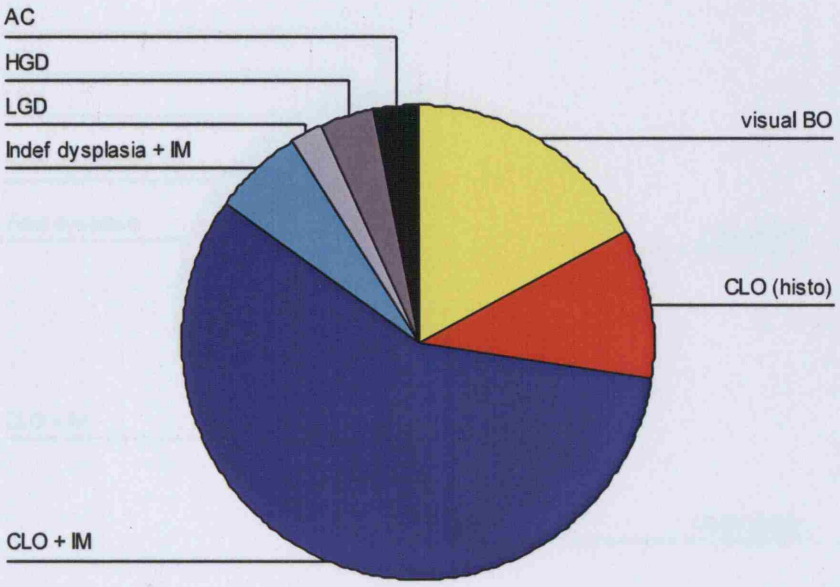
Proportions of HGD/AC ranged from 0.8% -6.7% of all grades of disease diagnosed, however; there were no significant differences on chi-square analysis ($p=0.134$). (nor when analysed separately - $p=0.061$, HGD and $p=0.482$, AC, chi-square)

Figures 24 a-f Distribution of grades of disease between centres

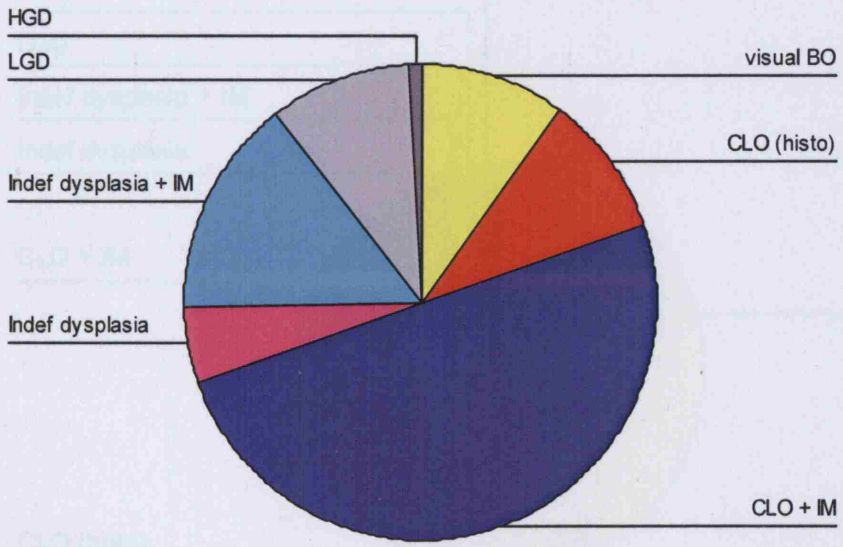




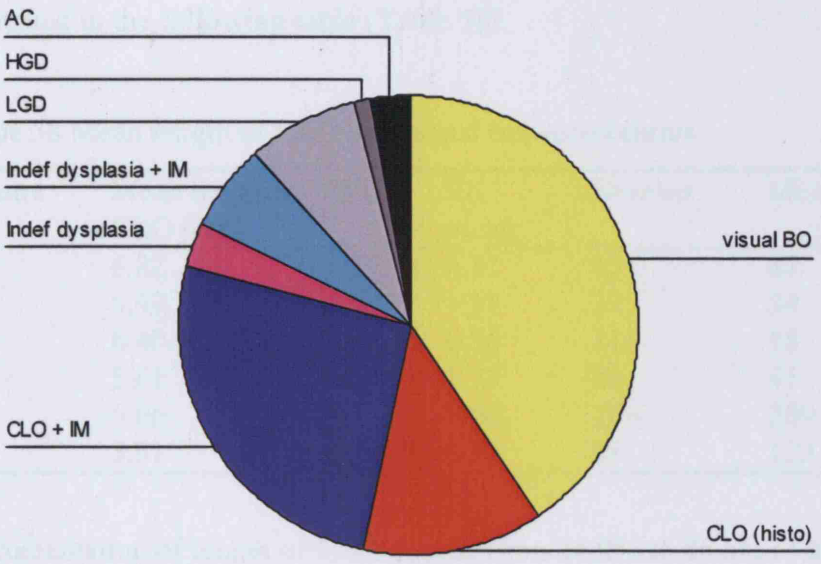
CENTRE: 3



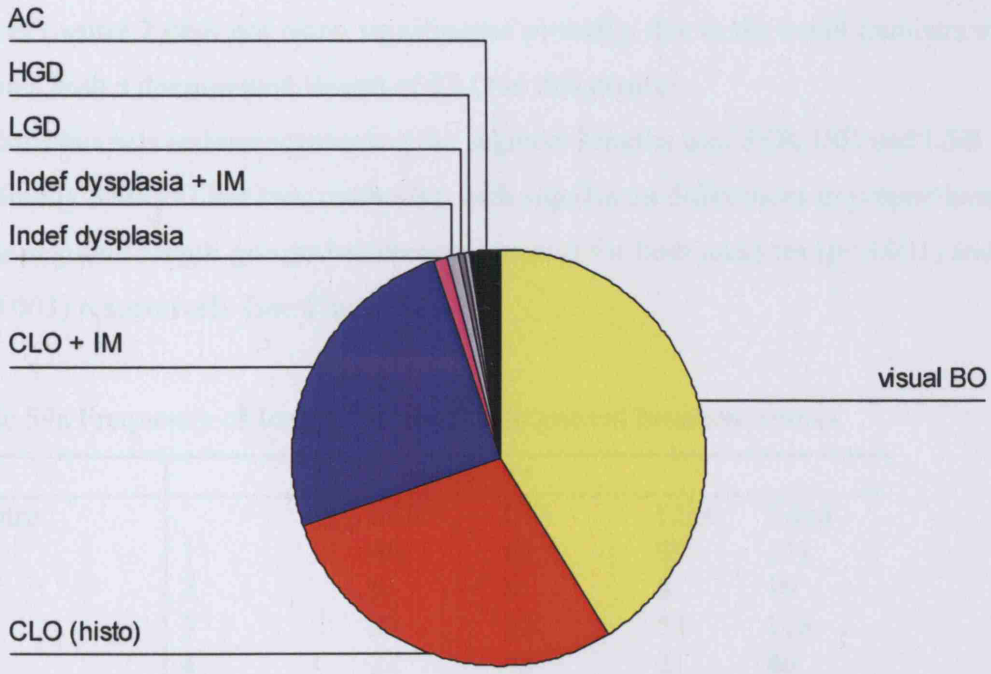
CENTRE: 4



CENTRE: 5



CENTRE: 6



Mean Length of CLO between centres:

The mean length of CLO for all grades of disease as diagnosed between centres is presented in the following table (Table 58).

Table 58 Mean length of CLO diagnosed between centres

Centre	Mean length CLO (cm)	STD	SE mean	Number	Missing	Percentage documented
1	6.82	4.25	0.33	171	87	66.3
2	6.97	4.84	1.11	19	54	26.0
3	6.40	3.25	0.30	116	18	86.6
4	5.61	3.09	0.33	86	45	65.6
5	5.06	3.31	0.20	266	209	56.0
6	5.51	3.31	0.35	88	123	41.7

Documentation of length of CLO ranged from 26.0% to 86.6% of all patients diagnosed between the centres, with an average frequency of documentation of 58.2%. There is a significant difference between mean length of CLO diagnosed between the 6 centres with centres 1 being significantly longer ($p<0.001$) and 5 being significantly shorter ($p<0.001$) when compared separately with the other centres (centre 2 does not reach significance probably due to the small numbers of patients with a documented length of CLO in this centre).

The analysis was redone regrouping the segment lengths into SSB, ISB and LSB and finally SSB vs LSB (see methods), with significant differences in proportions of the segment length groups between the centres for both analyses ($p<0.001$) and ($p=0.003$) respectively (see Figure 25).

Table 59a Frequency of lengths of disease diagnosed between centres

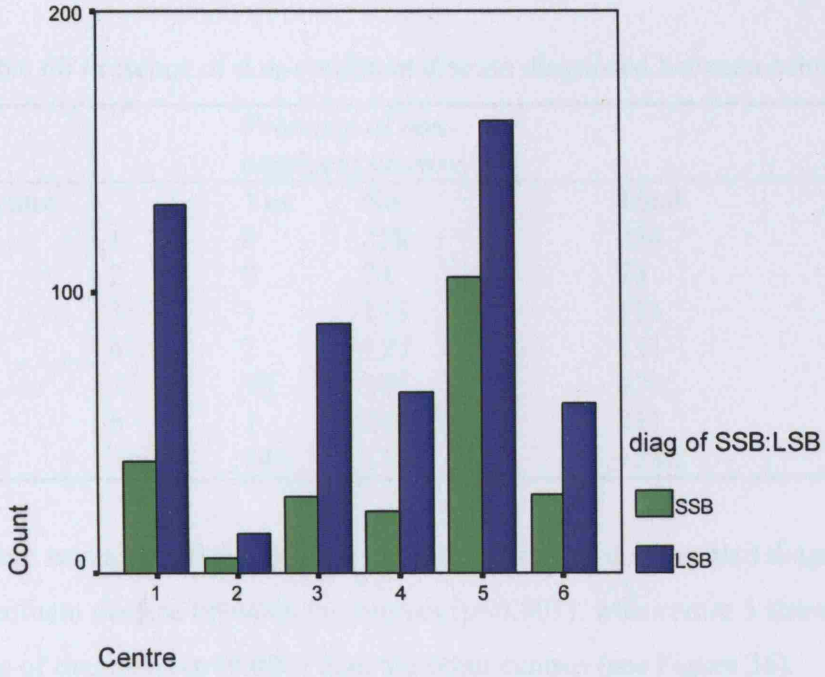
	Length CLO			
Centre	SSB	ISB	LSB	Total
1	40	62	69	171
2	5	6	8	19
3	27	35	54	116
4	22	43	21	86
5	105	89	72	266
6	28	32	28	88
Total	227	267	252	746

Table 59b

	Length CLO		
Centre	SSB	LSB	Total
1	40	131	171
2	5	14	19
3	27	89	116
4	22	64	86
5	105	161	266
6	28	60	88
Total	227	519	746

When analysed separately (SSB vs LSB analysis) the findings agree with the above results; centre 1 appears to have a significantly higher proportion of LSB ($p=0.023$) and centre 5, a significantly higher proportion of SSB ($p<0.001$, chi-square).

Figure 25 Diagnosis of SSB:LSB between centres



Diagnosis of non-confluent disease between centres.

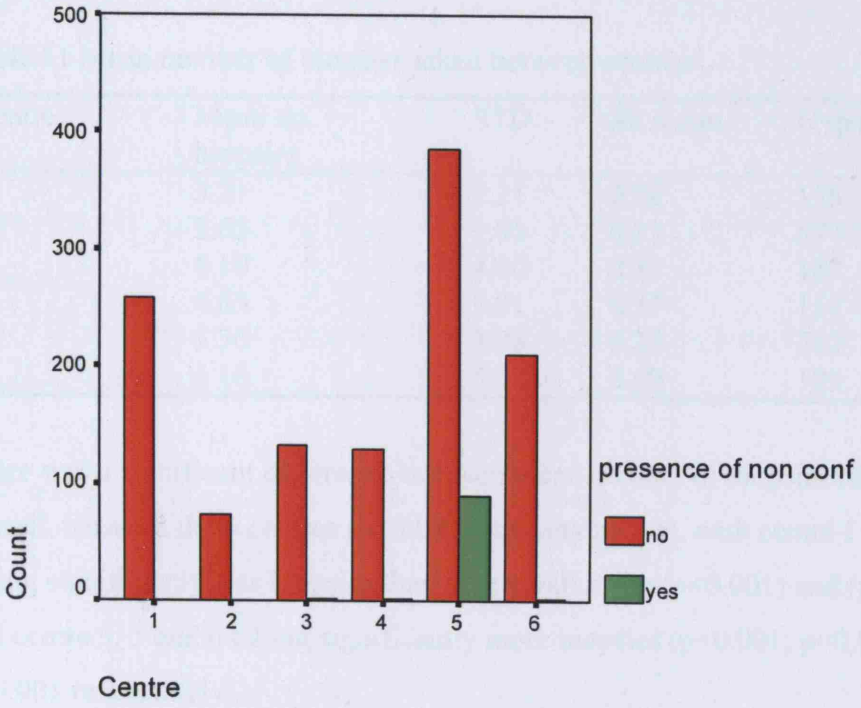
The table below represents the frequency of diagnosis of non-confluent disease between the 6 centres.

Table 60 Presence of non-confluent disease diagnosed between centres

		Presence of non-confluent disease		
Centre		Yes	No	Total
	1	0	258	258
	2	0	73	73
	3	1	133	134
	4	2	129	131
	5	90	385	475
	6	1	210	211
	Total	94	1188	1282

There was a significant difference in frequency of documented diagnosis of non-confluent disease between the centres ($p<0.001$), with centre 5 showing a higher rate of diagnosis ($p<0.001$) than the other centres (see Figure 26).

Figure 26 Diagnosis of non-confluent disease between centres



Number of biopsies

The mean number of biopsies taken for all disease diagnosed between the centres is presented below: (see Figure 27)

Table 61 Mean number of biopsies taken between centres

Centre	Mean no. biopsies	STD	SE mean	N (patients)
1	3.21	3.21	0.28	136
2	2.65	1.01	0.13	57
3	6.19	4.00	0.39	107
4	4.63	3.91	0.37	112
5	5.30	3.78	0.23	262
6	6.10	5.12	0.50	105

There was a significant difference between mean number of biopsies taken overall, between the 6 centres ($p<0.001$, one-way anova), with centre 1 and 2 taking significantly less biopsies than the overall mean ($p<0.001$) and ($p<0.001$), and centre 3, 5 and 6 taking significantly more biopsies ($p<0.001$; $p=0.035$; $p=0.001$ respectively).

The analysis was redone examining mean biopsies taken for each specific grade of diagnosis and the following table produced: (NB diagnosis 1 left out)

Table 62a Mean number of biopsies taken per grade of disease between centres

		Diagnosis						
		2	3	4	5	6	7	8
Centre	1	3.11	3.46	2.33	2.75	3.20	3.00*	4.50
	2	2.48	2.71	-	3.00	2.50	-	4.00*
	3	3.54	6.14	-	7.14	11.00	8.00	6.00
	4	4.10	3.90	3.71	6.56	6.38	-	-
	5	4.46	4.80	4.00	4.93	7.60	9.20	7.38
	6	6.15	6.13	2.50	3.50	2.00*	-	11.50

* only one patient with biopsies taken

Centres 1 and 2 appeared to be taking significantly less biopsies for diagnoses 2, 3, and 6 (diag 2: $p=0.043$; $p=0.026$ diag 3: $p=0.003$; $p=0.007$ diag 6: $p=0.008$;

p=0.023) (one-way anova) with centre 1 also taking significantly less biopsies for diagnosis 4 (p=0.021).

The mean number of biopsies taken by centre 6 were significantly more than the other centres for diagnoses 2 (p<0.001) and 3 (p=0.006) (one-way anova).

Centre 5 took significantly more biopsies for diagnoses 4 (p=0.043) and 6 (p=0.006) (one-way anova), with Centre 3 also taking significantly more biopsies for diagnosis 3 (along with centre 6) (p<0.001).

There were no significant differences in mean number of biopsies taken for diagnoses 5, 7 or 8.

When diagnoses were regrouped into non-dysplastic CLO, Indefinite for dysplasia, LGD and HGD/AC the following means were obtained:

Table 62b Mean number of biopsies taken per grade of disease between centres

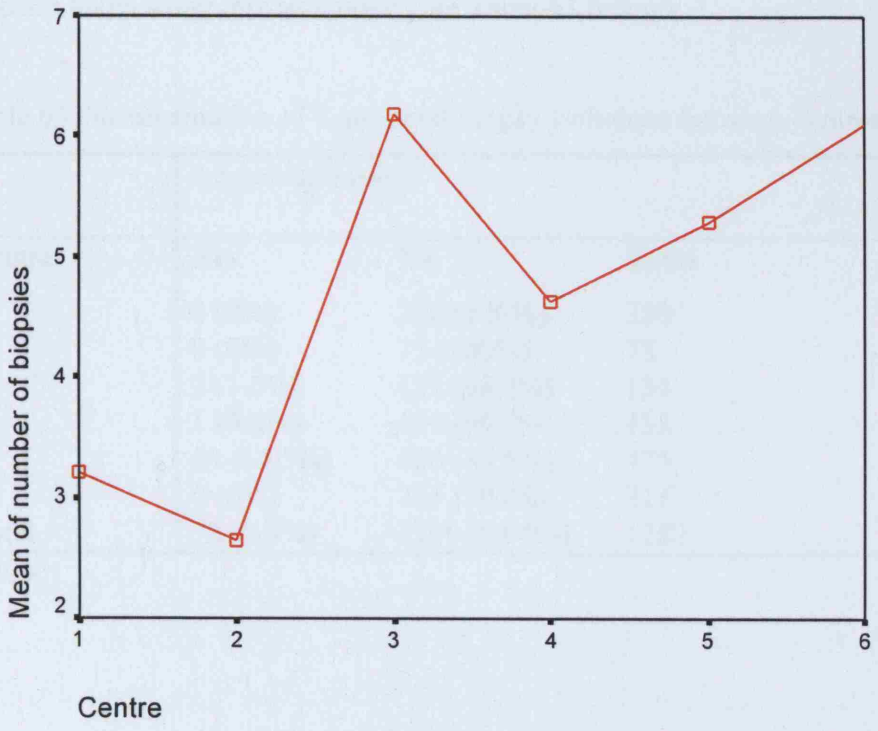
Centre	Non-dysp CLO	Indef dysp	LGD	HGD/AC
1	3.23	2.57	3.20	4.00
2	2.63	3.00	2.50	4.00*
3	5.88	7.14	11.00	7.00
4	3.95	5.76	6.38	-
5	4.70	4.65	7.60	7.89
6	6.16	3.00	2.00*	11.50

On one way anova; there was a significant difference between mean number of biopsies taken for non-dysplastic disease when the centres were compared (p<0.001), with centres 1 and 2 taking significantly less (p<0.001) (p<0.001) and centres 3 and 6 taking significantly more (p=0.001) (p<0.001)

There were no significant differences in mean number of biopsies taken between the centres for indefinite for dysplasia (diag 4+5) (p=0.078), LGD or HGD/AC.

For the overall diagnosis of non HGD/AC there were significant differences in the number of biopsies taken between the centres (p<0.001, one-way anova) with centres 1and 2 taking significantly less numbers of biopsies (p<0.001 (p<0.001) and centres 3 and 6 taking significantly more (p<0.001) (p=0.001).

Figure 27 Means plot to show mean number of biopsies taken (all grades of disease) between centres



4 quadrant biopsy technique – comparison between the centres

Only one of the centres had evidence of regular biopsies taken using a '4 quadrant technique' at diagnostic endoscopy, with 14.5% of biopsies documented to have been taken using this method. 50% of centres had no documentation at all of any biopsies taken using this technique (see Table 63 below).

Table 63 Documentation of 4 quadrant biopsy technique between centres

	4 quadrant biopsy		
Centre	**Yes**	**No**	**Total**
1	0 (0%)	258 (100%)	258
2	0 (0%)	73 (100%)	73
3	2 (1.5%)	132 (98.5%)	134
4	1 (0.8%)	130 (99.2%)	131
5	69 (14.5%)	406 (85.5%)	475
6	0 (0%)	211 (100%)	211
Total	72 (5.6%)	1210 (94.4%)	1282

P<0.001

Helicobacter Pylori

Prevalence of H Pylori (HP) infection

Out of the 1000 patients examined 424 (42.4%) patients had documented evidence of HP status. Out of these, 238 (56.1%) either had evidence of being HP positive or had eradication therapy at some time over their follow up. 66 had eradication therapy with 20 having a documented HP negative status post treatment; 6 remained HP positive and 40 had no HP status documented in the notes post treatment.

HP pos

Of the 238 HP positive patients, the 40 who had received eradication therapy but had no evidence of a post treatment HP status, and the 20 that were successfully eradicated, were excluded from further analysis. This left 178 patients in the HP pos cohort. 72 (40%) were diagnosed as being HP positive on their first endoscopy that was diagnostic for CLO; 99 (56%) were diagnosed after their diagnosis of CLO (an average of 5.36 years post diagnosis) and 8 (5%) before their diagnosis.

HP neg

190 patients had documented evidence of being HP negative. The 20 who had received successful eradication therapy were not included in this cohort. 104 (55%) were diagnosed on same endoscopy as their diagnostic for CLO endoscopy; 68 (36%) were diagnosed after their diagnosis of CLO (an average of 4.71 years post diagnosis) and 18 (9%) before their diagnosis (an average of 2.17 years before).

Demography of cohorts

Basic demographic makeup of the cohorts was examined and a comparison made between them.

Gender makeup

The overall ratio of males to females for the 3 groups combined was 1.9:1, with all groups showing a predominantly higher proportion of males. There were no significant differences in gender makeup between the groups on further analysis of the 3 groups (p=0.389; chi-square); nor on direct comparison of the HP pos and HP neg groups alone (p=0.199, chi-square) (see Figure 28).

Table 64 Gender distribution between HP cohorts

	Gender		
H pylori group:	Male	Female	ratio
HP pos	121	57	2.1:1
HP neg	117	73	1.6:1
erad	14	6	2.3:1
total	252	136	1.9:1

P=0.389 (chi-square)

Age at diagnosis

Age at diagnosis was examined in all three cohorts and subsequent comparison between the groups showed no significant differences (p=0.336; one-way anova) (between HP pos and HP neg : p = 0.148 on t-test; CI –0.7-4.7).

Table 65 Mean age at diagnosis of CLO between HP cohorts

H pylori group;	Mean age (years)	Std dev	SE mean
HP pos	60.45	13.25	0.99
HP neg	58.42	13.56	0.98
HP erad	60.19	13.56	2.72

P=0.336 (chi-square)

Follow-up period

The mean endoscopic follow-up period ranged from 3.35-5.39 years between the 3 cohorts and was significantly longer in the HP pos group (p<0.001, one way anova –all 3 groups; p<0.001, indep T – HP pos vs HP neg).

Figure 28 Pie charts showing gender distribution between the HP cohorts

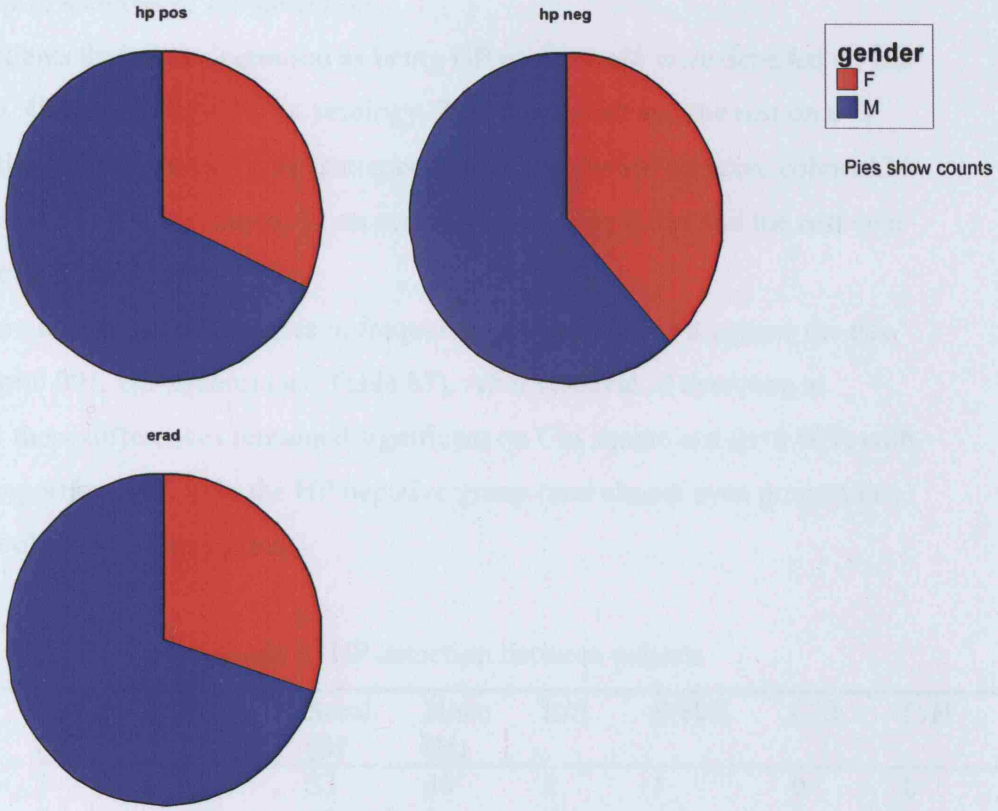


Table 66 Mean follow-up period between HP cohorts

HP group	Mean FU (years)	
HP pos	5.39	Std = 5.07
HP neg	3.35	Std = 4.03
HP erad	3.88	Std = 4.03

Frequency of methods of HP detection

Of the patients that were diagnosed as being HP positive, 48 were detected on Clo test alone, 49 on histology, 53 on serology, 3 on breath test and the rest on a combination of these tests. Of the patients included in the HP negative cohort 124 were detected on Clo test alone, 52 on serology, 5 on breath test and the rest on a combination of these tests.

There were significant differences in frequency of tests used to diagnose the two cohorts ($p<0.001$, chi-square) (see Table 67). After removal of detection at histology these differences remained significant on Chi square test ($p<0.001$) with higher proportions of Clo in the HP negative group (and almost even proportions of Clo:serol in the HP pos group).

Table 67 Frequency of methods of HP detection between cohorts

HP	Breath (B)	Clo (C)	Serol (S)	Histo (H)	B/S	B/H/S	C/B	C/H
Pos	3	48	53	49	2	1	0	6
Neg	5	124	52	0	2	0	1	0

P<0.001 (chi-square)

Smoking

Data on smoking was extracted from the database as classified by the smoking score previously defined.

On initial analysis (all categories) there were no significant differences in proportions of categories of smoker between the HP pos and HP neg cohorts ($p=0.056$; chi-square).

When smoking data were further analysed re-classifying the smoke score into two categories – category 1 including all 'ex-smokers' and 'non-smokers', and

category 2 including all 'current smokers'(see methods) - there remained no significant differences in smoking habits between the 3 cohorts (p=0.972, chi-square) nor between the HP pos and HP neg groups when analysed separately (p=0.796, chi-square).

On further analysis into three smoking categories (see methods) there remained no significant differences between the three cohorts (p=0.998; chi-square)

Alcohol

Data on alcohol consumption were classified as previously described (see methods) and analyses between the three cohorts were undertaken.

Initial analyses showed no significant differences between the 3 cohorts (p=0.393; chi-square) but a significant difference on comparison between just the HP pos and HP neg cohorts (p=0.026; chi-square).

On further analysis, however, re-classifying alcohol use into heavy/excessive vs moderate/mild (see methods), there were no significant differences between the 3 cohorts (p=0.980, chi-square) nor between the HP pos and HP neg grouped when examined separately (p=0.067; chi-square).

Diagnostic pathology

Length of CLO segment

The mean length of columnarised segment in the HP pos group was 5.43cm, and 4.89cm in the HP neg group, with no significant difference on statistical analysis (p=0.227; indep-T) (see Figure 29).

Table 68 Mean length of CLO at diagnosis between cohorts

	mean	Std dev	SE mean
HP pos	5.43	3.246	0.338
HP neg	4.89	3.109	0.302

p = 0.227 (indep T-test) (CI 0.34 – 1.44) (HP+ vs HP-)

On repeat analysis by segment length (see methods), there remained no significant difference between the HP pos and HP neg groups (p=0.758; chi-square).

Figure 29 Error bars showing mean lengths of CLO at diagnosis between HP cohorts

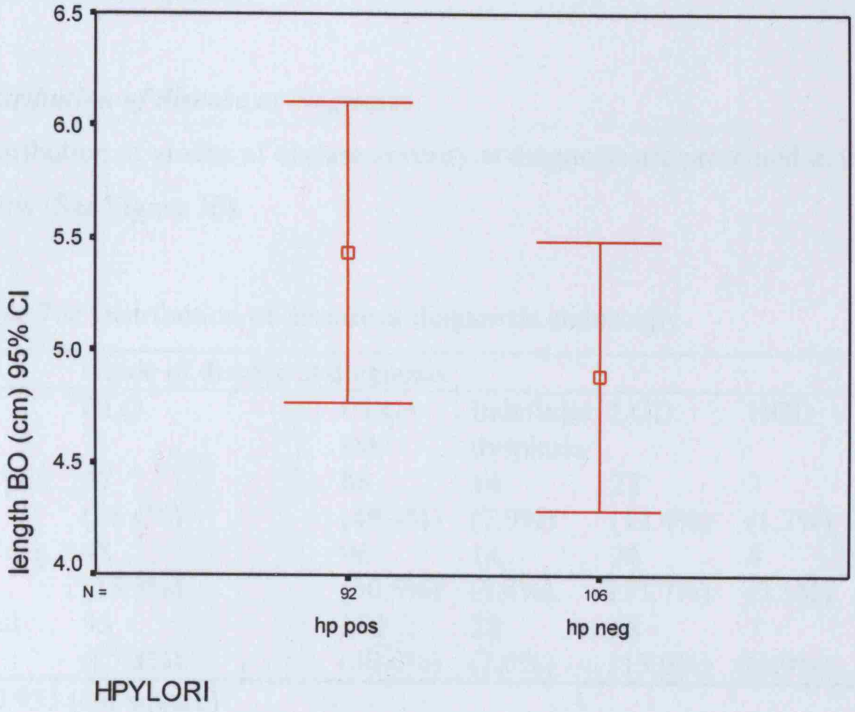


Table 69 Frequency of lengths of CLO diagnosed between cohorts

	Segment length category		
	Short	Intermediate	Long
HP pos	36	34	28
HP neg	35	45	29

p = 0.758 (chi-square)

Distribution of disease at diagnosis

Distribution of grades of disease severity at diagnosis are presented in the tables below (See Figure 30).

Table 70a Distribution of disease at diagnostic endoscopy

	Grade of disease at diagnosis						
	CLO	CLO+ IM	Indefinite dysplasia	LGD	HGD	AC	Total
HP pos	47 (26.4%)	88 (49.4%)	14 (7.9%)	22 (12.4%)	3 (1.7%)	4 (2.2%)	178
HP neg	48 (25.3%)	96 (50.5%)	14 (7.4%)	26 (13.7%)	4 (2.1%)	2 (1.1%)	190
Total	95 (25.8%)	184 (50.0%)	28 (7.6%)	48 (13.0%)	7 (1.9%)	6 (1.6%)	368

p=0.953 (chi-square)

Table 70b Distribution of disease at diagnostic endoscopy, regrouped

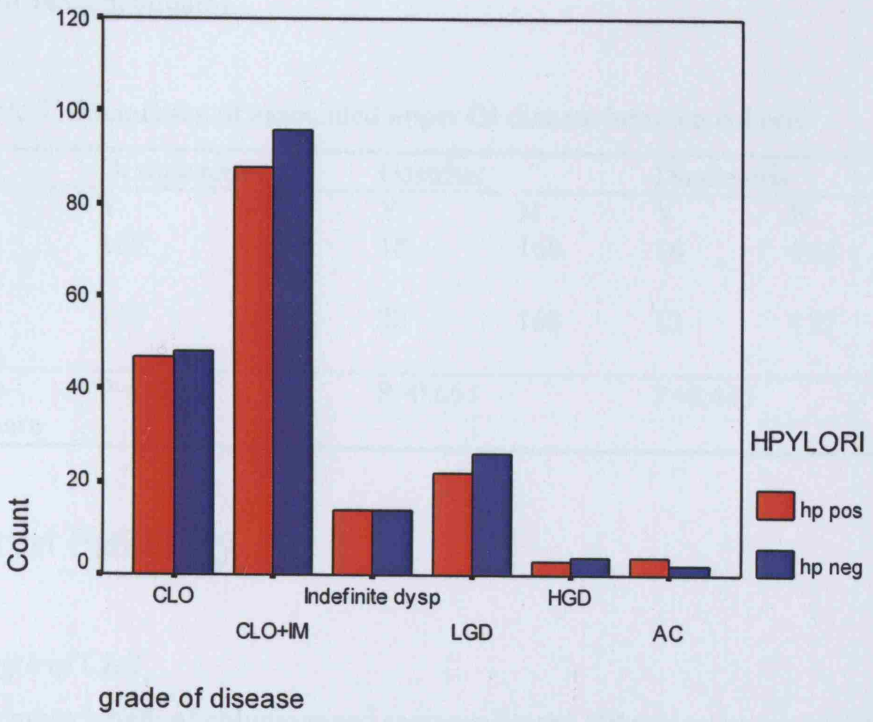
	Grade of disease at diagnosis		Total
	Non-dysp CLO	dysplastic CLO	
HP pos	171 (96.1%)	7 (3.9%)	178
HP neg	184 (96.8%)	6 (3.2%)	190
Total	355 (96.5%)	13 (3.5%)	368

P=0.687 (chi-square)

Proportions of grades of disease were similar between the 2 cohorts with no significant differences in distribution at diagnosis on initial analysis (p=0.953) or on further analysis re-categorising disease into non-dysplastic and severely dysplastic groups (HGD/AC) (p=0.687)

Figure 30

Bar chart to show distribution of grades of disease at diagnosis between HP cohorts



Oesophagitis/gastritis/duodenitis

On examination of frequency of associated oesophagitis at diagnostic endoscopy there were no significant differences between the two groups (p=0.994; chi-square).

The frequency of gastritis/gastric ulceration associated with CLO was similar between the two groups (p=0.651), as was duodenitis/duodenal ulceration (p=0.445, chi-square).

Table 71 Frequency of associated upper GI disease between cohorts

	Oesophagitis		Gastritis		Duodenitis	
	Y	N	Y	N	Y	N
HP pos	105	73	18	160	16	162
HP neg	112	78	22	168	13	177
Chi-square	P=0.994		P=0.651		P=0.445	

Worst Pathology

Length of CLO

The mean length of columnarised segment for the HP pos group was 6.19cm, 5.79cm for the HP neg group and 4.62cm for the HP erad group, with no significant differences between them (p=0.199; one-way anova). On analysis of length of CLO between the HP pos and HP neg groups alone there remained no significant differences (p=0.305; Indep T, p=0.269; Mann Whit) (See Figures 31a,b)

Table 72 Mean length of CLO at worst pathology between cohorts

	Mean length CLO	Std dev	SE mean
HP pos	6.19	3.310	0.271
HP neg	5.79	3.315	0.283
HP erad	4.62	2.987	0.828

p = 0.199 (one-way anova)

Figure 31a Error bar charts showing mean lengths of CLO at worst pathology between HP cohorts

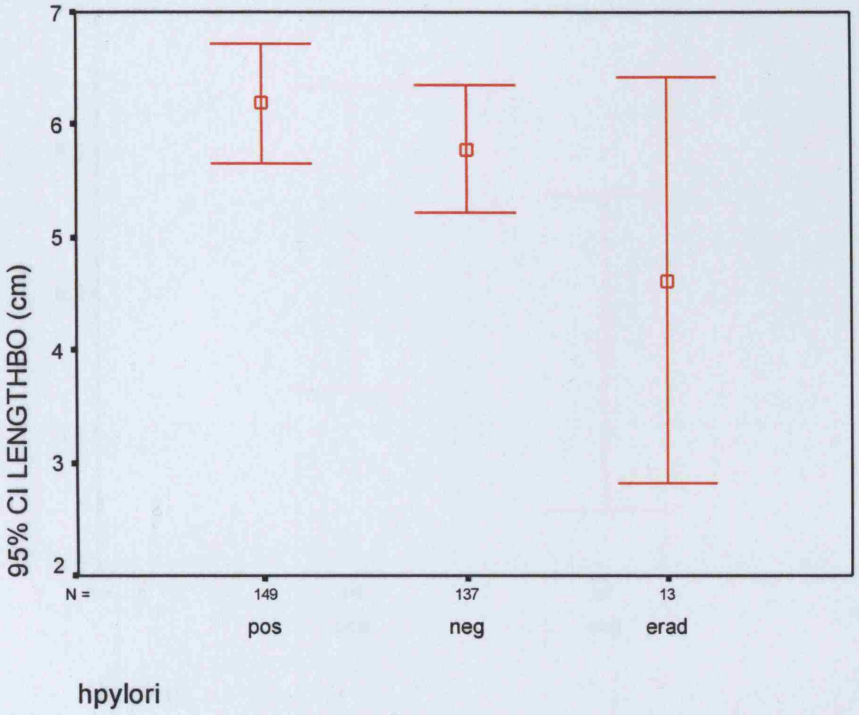
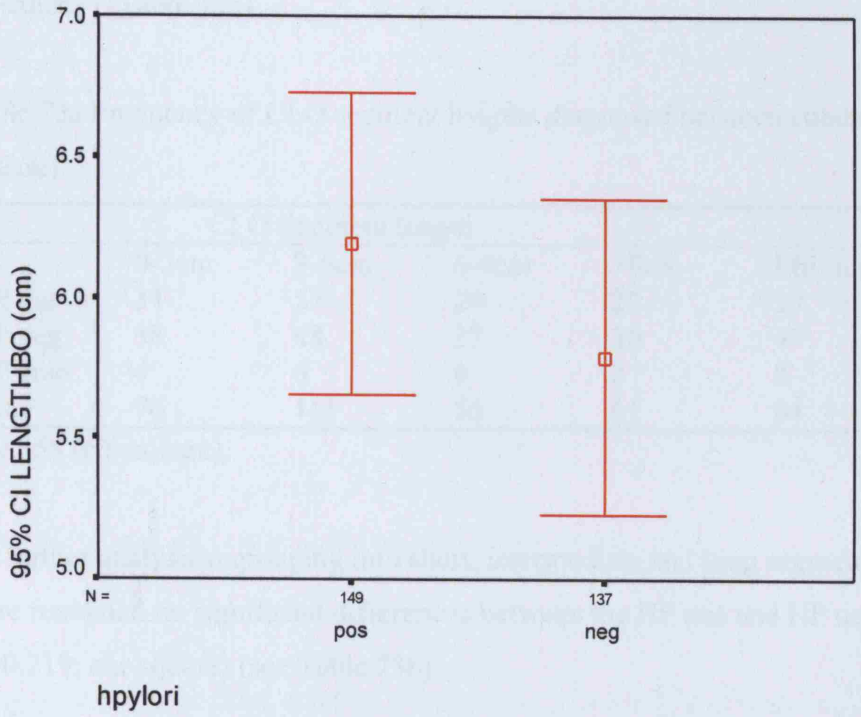


Figure 31b Error bar charts of mean length of CLO between HP+ and HP- cohorts



On analysis regrouping into the 4 segment length categories (see methods), there were no significant differences in length between the 3 cohorts (p=0.358; chi-square) nor when the HP pos and HP neg groups were analysed separately (0.399; chi-square) (Table 73a).

Table 73a Frequency of CLO segment lengths diagnosed between cohorts (worst disease)

	CLO Segment length					
	0-3cm	3-6cm	6-9cm	>9cm	Missing	Total
HP pos	34	57	29	29	29	178
HP neg	38	48	27	30	47	190
HP erad	4	6	0	2	8	20
Total	76	111	56	61	84	388

P=0.358 (chi-square)

On further analysis regrouping into short, intermediate and long segment disease there remained no significant differences between the HP pos and HP neg groups (p=0.219; chi-square) (see Table 73b).

Table 73b

	Segment length category		
	Short	Intermediate	Long
HP pos	36	55	59
HP neg	38	49	57

p = 0.219 (chi-square)

Presence of oesophagitis/gastritis/duodenitis

There was a significant difference in frequency of associated oesophagitis at worst pathology when all 3 cohorts were compared (p<0.001, chi-square) with much less in the HP erad cohort. However, when just the HP pos and HP neg cohorts were compared the frequency of oesophagitis was very similar, with no significant difference on chi square (p=0.583, chi-square).

On examination of associated presence of gastro-duodenal inflammation and/or ulceration there were no significant differences between the 3 cohorts, nor on

comparison of the HP pos and HP neg groups alone (see table 75). However, there was a trend for there to be less associated gastro-duodenal disease in the HP erad group, although this did not quite reach statistical significance.

Table 74 Associated upper GI disease at worst pathology between HP cohorts

	Oesophagitis		Gastritis		Duodenitis	
	Yes	No	Yes	No	Yes	No
HP pos	141 (79.2%)	37 (20.8%)	48 (27.0%)	130 (73.0%)	38 (21.3%)	140 (78.7%)
HP neg	146 (76.8%)	44 (23.2%)	43 (22.6%)	147 (77.4%)	29 (15.3%)	161 (84.7%)
HP erad	3 (15.0%)	17 (85.0%)	1 (5.0%)	19 (95.0%)	3 (15.0%)	17 (85.0%)
†	P<0.001		P=0.081		P=0.296	
*	P=0.583		P=0.335		P=0.131	

† comparison of all 3 cohorts, chi-square

* comparison of HP pos and HP neg only, chi-square

Disease distribution

Distribution of worst disease between the groups is presented in the table below: (see Figures 32a,b)

Table 75 Distribution of worst pathology between HP cohorts

	Histological grade of disease						
	CLO	CLO + IM	Indefinite dysplasia	LGD	HGD	AC	Total
HP pos	20 (11.2%)	65 (36.5%)	33 (18.5%)	50 (28.1%)	3 (1.7%)	7 (3.9%)	178
HP neg	32 (16.8%)	76 (40.0%)	24 (12.6%)	43 (22.6%)	7 (3.7%)	8 (4.2%)	190
HP erad	4 (20.0%)	12 (60.0%)	0 (0%)	4 (20.0%)	0 (0%)	0 (0%)	20
Total	56 (14.4%)	153 (39.4%)	57 (14.7%)	97 (25.0%)	10 (2.6%)	15 (3.9%)	388

P=0.156 † (chi-square)

P=0.231 * (chi-square)

There were no significant differences in distribution of grades of disease on worst pathology on comparison of all 3 cohorts † (p=0.156; chi-square) and when just the HP pos and HP neg groups compared * (p=0.231; chi-square).
On further analysis reclassifying disease into non-HGD/AC and HGD/AC there remained no significant differences in distribution of disease severity between the 3 cohorts (p=0.326; chi-square) nor on comparison of the HP pos and HP neg groups alone (p=0.386; chi-square).

Figure 32a Bar chart showing distribution of worst disease between HP cohorts

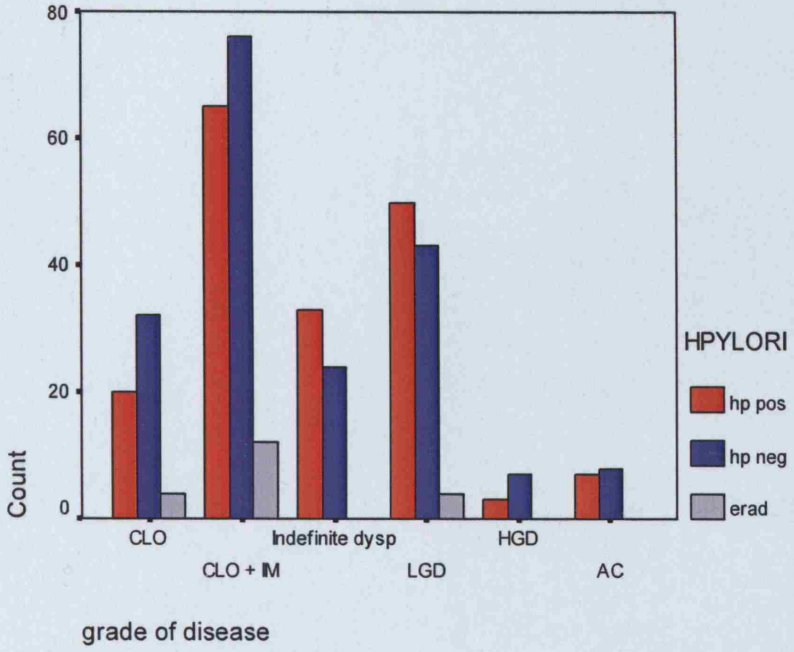
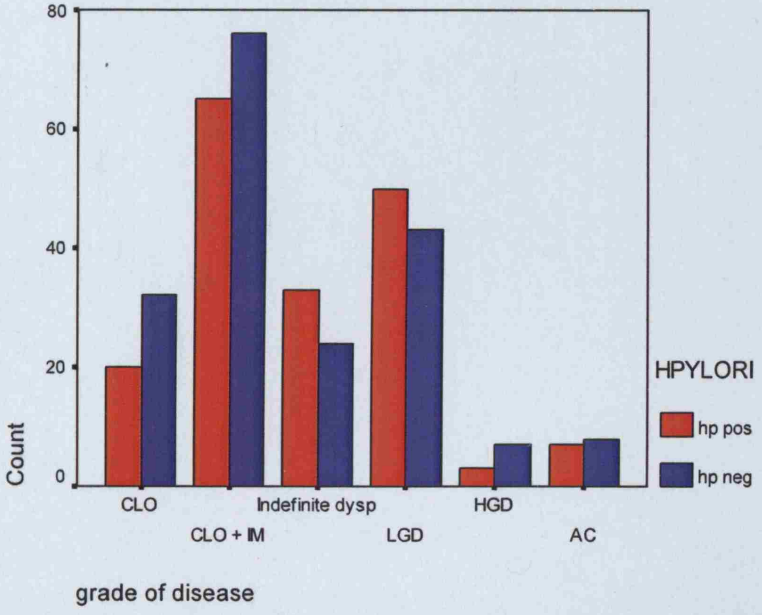


Figure 32b



Surveillance

1. Centre Demographics

Surveillance proportion

817 (63.7%) patients had documentation of being on a surveillance programme and had undergone more than 1 follow-up endoscopy, thus fulfilling the criteria for inclusion in the surveillance cohort (overall mean number of endoscopies performed whilst on surveillance was 5).

They were all enrolled onto programmes between April 1978 and February 2003. The proportion of patients surveyed and endoscopic follow-up period throughout the entire cohort and in each individual centre is presented in the table below: (see Figure 33)

Table 76 Proportion of patients under surveillance

Centre	Total patients N	Number on surveillance N (%)	Diagnostic OGD only N (%)	No surveillance N (%)	Mean OGDs
1	258	70 (27.1)	179 (69.4)	9 (3.5)	3
2	73	51 (69.9)	22 (30.1)	0 (0)	4
3	134	57 (42.5)	77 (57.5)	0 (0)	3
4	131	94 (71.8)	37 (28.2)	0 (0)	4
5	475	374 (78.7)	93 (19.6)	10 (2.1)	8
6	211	171 (81.0)	40 (19.0)	1 (0.5)	6
Total	1282	817 (63.7)	445 (34.7)	20 (1.6)	5

Figure 33 Pie chart showing proportion of patients under surveillance

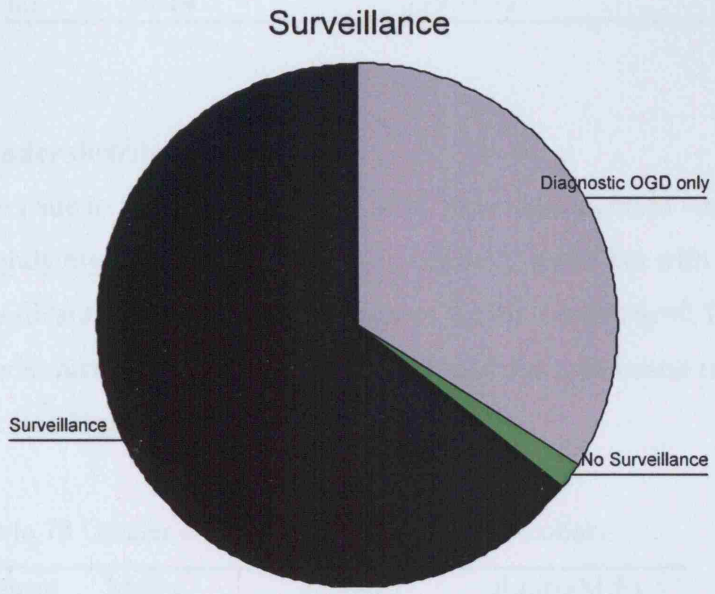


Table 77 Number of OGDs and endoscopic follow-up between centres

Centre	Total no. OGDS	Total FU (years)
1	232	170.23
2	193	163.88
3	143	143.08
4	377	282.94
5	2902	2394.17
6	967	799.17
Total	4814	3953.17

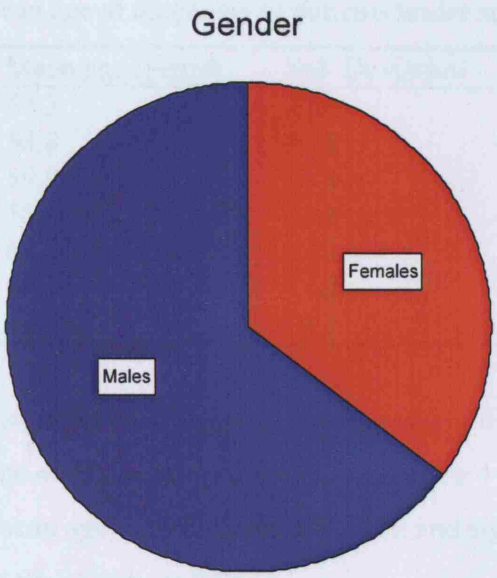
Gender distribution

The male to female ratio of the entire surveillance cohort was 1.8:1, with a slightly higher male:female ratio in centres 2 and 3 but with no statistically significant differences between any of the six centres (p=0.327; chi-square). The gender distribution of the entire cohort and for each centre is presented in table 78. (see Figure 34)

Table 78 Gender distribution of surveillance cohort

Centre	Males n (%)	Females n (%)	Ratio (M:F)
1	46 (65.7)	24 (34.3)	1.9
2	36 (70.6)	15 (29.4)	2.4
3	44 (77.2)	13 (22.8)	3.4
4	62 (66.0)	32 (34.0)	1.9
5	235 (62.2)	139 (36.8)	1.7
6	106 (62.0)	65 (38.0)	1.6
Total	529 (64.7)	288 (35.3)	1.8

Figure 34 Pie chart showing gender distribution of surveillance cohort



Age at diagnosis

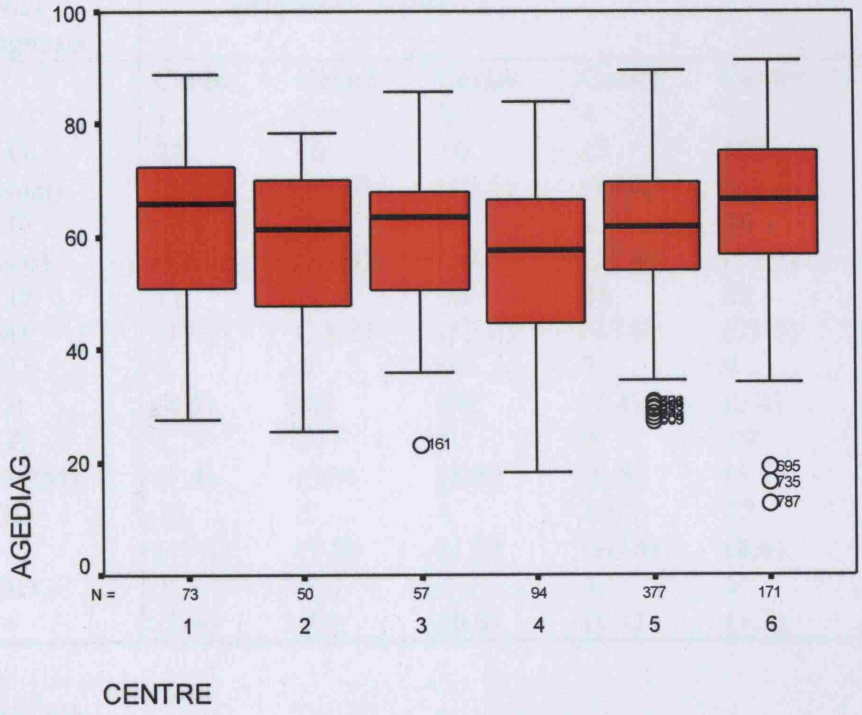
The mean age at initial/diagnostic endoscopy of the entire cohort was 61.2 years, with males being diagnosed at a slightly earlier age, 59.4 years, compared with females at 64.6 years (p=0.016, indep T). The mean age at diagnosis for all centres is presented in the following table: (see Fig 35)

Table 79 Mean age at diagnosis of patients under surveillance between centres

Centre	Mean age (years)	Std. Deviation	SE of Mean	95% CI
1	62.3	13.6	1.6	59.2-65.5
2	58.8	14.6	2.0	54.6-63.0
3	59.8	13.4	1.8	56.2-63.3
4	55.8	13.0	1.3	53.1-58.4
5	61.2	12.2	0.6	59.9-62.4
6	65.1	13.6	1.0	63.1-67.2
overall	61.2	13.2	0.5	

There were significant differences in mean age at diagnosis between the centres ($p<0.001$, one-way anova) with patients in centre 4 being significantly younger at diagnosis (mean age = 55.8 years, $p<0.001$), and significantly older in center 6 (mean age = 65.1 years, $p<0.001$).

Figure 35 Mean age (years) at diagnosis of patients under surveillance between centers



Disease distribution

The distribution of disease subtypes at diagnosis were classified as according to Table 9a, methods, and are presented in the table below (see Figure 36a).

Table 80a Frequency of disease distribution at diagnosis between centres

Initial diagnosis	*Frequency N (%)*					
	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
CLO (visual)	23 (32.9)	10 (19.6)	10 (17.5)	13 (13.8)	182 (48.7)	70 (40.9)
CLO (histo)	17 (24.3)	16 (31.4)	6 (10.5)	13 (13.8)	44 (11.8)	49 (28.7)
CLO (IM)	12 (17.1)	18 (35.3)	30 (52.6)	41 (43.6)	82 (21.9)	46 (26.9)
CLO (ID)	3 (4.3)	0 (0)	0 (0)	7 (7.4)	9 (2.4)	2 (1.2)
CLO (ID+IM)	1 (1.4)	2 (3.9)	5 (8.8)	9 (9.6)	19 (5.1)	2 (1.2)
LGD	12 (17.1)	5 (9.8)	1 (1.8)	10 (10.6)	32 (8.6)	1 (0.6)
HGD	1 (1.4)	0 (0)	5 (8.8)	1 (1.1)	5 (1.3)	1 (0.6)

Table 80b

Initial diagnosis	*Frequency N (%)*					
	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
Non-dysplastic CLO	56 (80.0)	46 (90.2)	51 (89.5)	83 (88.3)	336 (89.8)	169 (98.8)
LGD	12 (17.1)	5 (9.8)	1 (1.8)	10 (10.6)	32 (8.6)	1 (0.6)
HGD	1 (1.4)	0 (0)	5 (8.8)	1 (1.1)	5 (1.3)	1 (0.6)

Table 80c Distribution of worst disease per centre (see Figure 37b)

Centre	Non-dysplastic CLO	LGD	HGD	AC
1	46 (65.7%)	19 (27.1%)	3 (4.3%)	2 (2.9%)
2	29 (56.9%)	18 (35.3%)	1 (2.0%)	3 (5.9%)
3	44 (77.2%)	7 (12.3%)	4 (7.0%)	2 (3.5%)
4	58 (61.7%)	34 (36.2%)	1 (1.1%)	1 (1.1%)
5	246 (65.8%)	90 (24.1%)	14 (3.7%)	24 (6.4%)
6	156 (91.2%)	10 (5.8%)	1 (0.3%)	3 (0.8%)
Total	579 (70.9%)	178 (21.8%)	24 (2.9%)	35 (4.3%)

Indefinite for dysplasia

Proportions of patients at diagnostic endoscopy with indefinite for dysplasia varied significantly between centres (p=0.001; chi-square), with centre 4 showing a significantly higher proportion of indefinite for dysplasia when compared to the other centres (*p<0.001; chi-square), and centre 6 significantly less (†p=0.006) (see Table 81).

Table 81 frequency of indefinite for dysplasia between centers

Centre	*Indef dysplasia*	*Non- indef dysplasia*	*Total*
1	4 (5.71%)	66 (94.29%)	70
2	3 (5.88%)	48 (94.12%)	51
3	5 (8.77%)	52 (91.23%)	57
4	16 (17.02%)*	78 (82.98%)	94
5	28 (7.49%)	349 (93.32%)	374
6	4 (2.34%)†	167 (97.66%)	171
Total	59 (7.18%)	763 (92.82%)	817

Figure 36a Distribution of grades of disease at diagnosis between centers

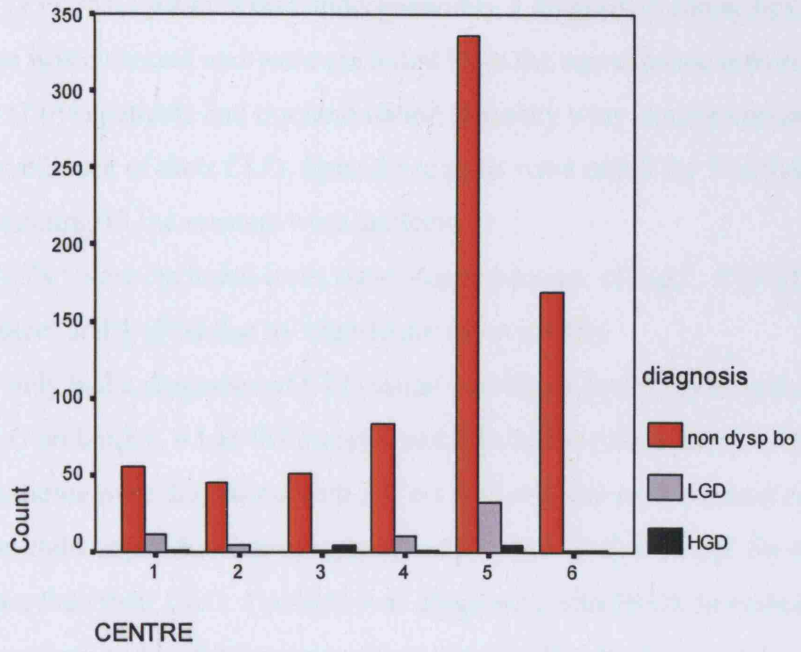
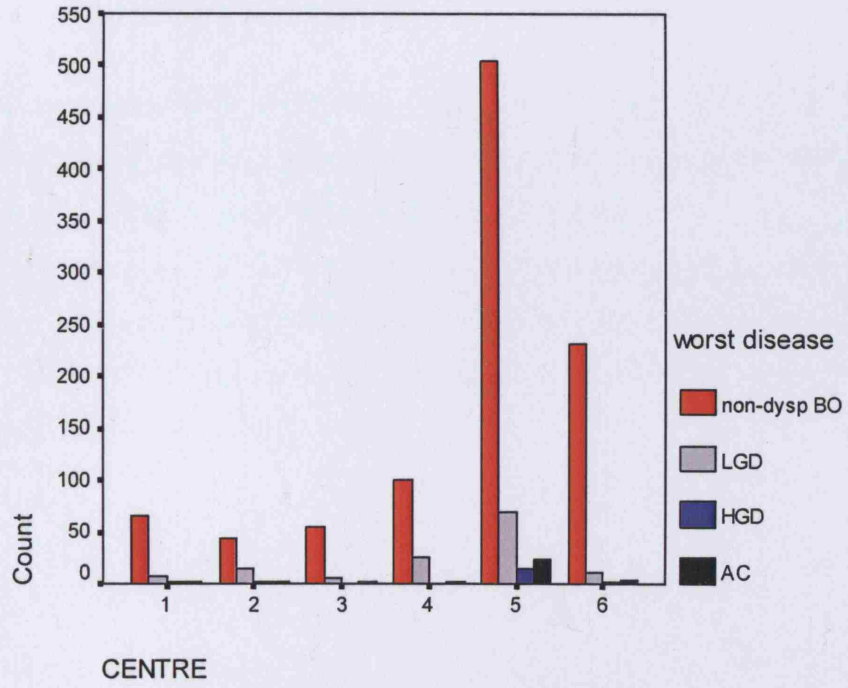


Figure 36b Distribution of grades of disease at worst diagnosis between centres



'Non-surveillance' group

433 (33.78%) patients had undergone only 1 diagnostic endoscopy at the time the data was collected and were excluded from the surveillance cohort.

20 (1.6%) patients had documentation that they were not for endoscopic surveillance of their CLO. Specific reasons were noted for 7 of them; and in the remaining 13 the reasons were unclear.

5 (25%) were excluded from surveillance because of 'age', 1 (5%) due to 'patient choice' and 1 (5%) due to 'significant co-morbidity'.

11 only had a diagnosis of CLO made visually, 4 had histological confirmation of CLO on biopsy, 4 had IM present, and 1 had IM with indefinite for dysplasia.

3 patients were diagnosed with AC on further (non-surveillance) endoscopy; 1 was endoscoped for new symptoms and 2 were 'followed-up' for other reasons other than their CLO. 1 patient was diagnosed with HGD on endoscopy for new symptoms and underwent oesophagectomy with a histological diagnosis of AC post-operatively.

3 of these patients died (with cause of death related to AC).

Table 82 Details of patients documented as 'not for surveillance'

Patient	Progress to HGD/AC	outcome	survival	Cause of death
1	Y	A	9.89	-
2	N	D	8.64	unclear
3	N	A	0.29	-
4	N	A	5.39	-
5	N	A	8.15	-
6	N		1.45	-
7	N	A	6.63	-
8	N	D	0.88	'old age'
9	Y	D	2.34	AC
10	Y	D	2.41	AC
11	N	A	8.51	-
12	N	D	3.22	Gangrene (leg)
13	N	A	-	-
14	N	A	-	-
15	N	A	-	-
16	Y	D	5.42	AC
17	N	A	-	-
18	N	A	0.13	-
19	N	A	-	-
20	N	A	1.53	-

The mean age of the patients at diagnosis was 72.6 years (STD 11.32, SE mean 2.53). In comparison with the patients in the surveillance group (mean age 61.23) they were significantly older ($p<0.001$, indep T-test).

The mean length of CLO documented at diagnosis was 6.00 cm (STD 3.66, SE mean 1.10) which was less but not significantly different than the mean length of CLO diagnosed in the surveillance group (8.94 cm) ($p=0.551$, indep T-test).

e) Endoscopic Interval

A total of 4819 endoscopies were performed on the 817 patients undergoing surveillance; spanning an endoscopic follow-up period of 3953.47 years. The mean number of endoscopies performed over the follow-up period per patient approximated to 5.

The mean endoscopic intervals varied throughout the centres from 1.07 to 1.63 years (approximately 13 to 20 months) for uncomplicated CLO (no dysplasia); 0.69 to 1.19 years (approximately 8 to 14 months) for LGD and 0.35 to 1.17 years (approximately 4-14 months) for HGD; with mean intervals being 1.29 (~15 months), 1.01 (~12 months) and 0.44 (~ 5 months) respectively.

The total numbers of grades of disease being surveyed was 1184. The table below shows the numbers of disease 'events' being surveyed for each of the centres.

Table 83 Numbers of disease events being surveyed between centres

	Centre						
Diagnosis	1	2	3	4	5	6	Total
CLO (visual)	23	10	10	13	182	69	307
CLO (histo)	17	17	6	13	86	70	209
CLO (IM)	12	20	33	42	175	89	371
CLO (ID)	4	0	0	8	24	4	40
CLO (ID+IM)	1	2	7	17	42	6	75
LGD	19	13	0	33	84	6	155
HGD	1	0	5	1	17	3	27
Total	77	62	61	127	610	247	1184

Exact mean endoscopic intervals, with standard deviation and SE of the mean, for all disease subtypes are presented in results table 84a; and the findings broken down into non-dysplastic CLO, LGD and HGD in table 84b (see Figure 37).

Table 84a Mean endoscopic surveillance intervals per grade of disease diagnosed

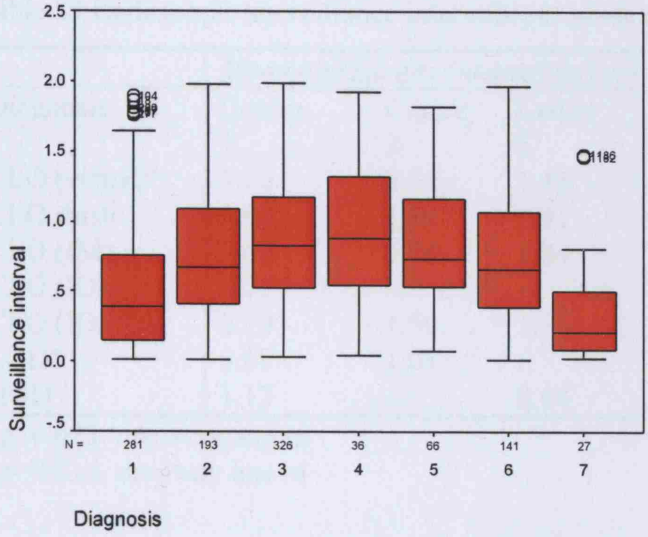
	Endoscopic surveillance interval (years)			
Diagnosis	Mean	STD	SE of mean	95% CI
CLO (visual)	1.14	1.71	0.10	0.94-1.33
CLO (histo)	1.19	0.95	0.07	1.06-1.32
CLO (IM)	1.42	1.10	0.06	1.31-1.53
CLO (ID)	1.36	1.18	0.19	0.98-1.74
CLO (ID+IM)	1.48	1.41	0.16	1.16-1.80
LGD	1.01	0.72	0.06	0.90-1.13
HGD	0.44	0.44	0.08	0.27-0.62

Table 84b

Diagnosis	*Mean*	*STD*	*SE of mean*	*95% CI*
Non-dysplastic CLO	1.29	1.32	0.04	1.20-1.37
LGD	1.01	0.72	0.06	0.90-1.13
HGD	0.44	0.44	0.08	0.27-0.62

There was a significant difference between mean endoscopic intervals for each of the disease subtypes being surveyed ($p<0.001$, one-way anova), with surveillance for HGD being significantly more frequent then for LGD and non-dysplastic disease.

Figure 37 Mean endoscopic surveillance intervals (years) per grade of disease surveyed



Comparison between centres

Mean surveillance intervals per diagnosis were analysed as a comparison between the centres. The results are presented for individual centres in Table 85.

Table 85 Endoscopic surveillance intervals per grade of disease, between centres

	Mean endoscopic interval (years)					
Diagnosis	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6
CLO (visual)*	1.76	2.10	1.43	1.94	0.99	0.97
CLO (histo)	1.00	1.14	0.91	0.77	1.33	1.17
CLO (IM)	1.68	1.24	1.84	1.15	1.58	1.07
CLO (ID)	2.75	-	-	0.75	1.45	0.70
CLO (ID+IM)	0.29	1.50	1.51	0.91	1.78	1.13
LGD†	0.69	1.01	-	0.80	1.19	0.74
HGD	1.17	-	0.44	0.58	0.35	0.69

* p=0.025, one-way anova
† p=0.016, one-way anova

On analysis, there were significant differences between mean surveillance intervals for disease subtypes 1 (p=0.025) and 6 (p=0.016) (one way analysis of variance) when the 6 centres were compared, with no significant differences for any other grades of disease. However, on regrouping diagnoses 1-5 into overall 'non-dysplastic disease' there were no longer any significant differences in mean surveillance interval between the centres for this category (p= 0.123).

f) Detection of dysplasia

A Total of 193 patients were diagnosed with LGD at some point; 61 on initial diagnostic endoscopy, 132 on subsequent follow up endoscopies. 178 patients had a diagnosis of LGD at their follow-up endpoint. Of the 132 patients picked up on follow-up endoscopy 125 (94.7%) were picked up on specific surveillance endoscopies; 5 were diagnosed having had endoscopies for new symptoms whilst on surveillance, in 1 the indication for endoscopy was unclear and 1 patient had undergone endoscopy for other 'follow-up' reasons other that CLO (eg. strictures/gastric ulcer etc..)

[NB. Analysis of HGD is presented later on in a separate section]

AC analysis

From the *surveillance* cohort a total of 35 cancers (AC) were diagnosed. They were all detected on follow-up endoscopies whilst under surveillance - although they were not all necessarily picked up on specifically documented surveillance endoscopies.

Table 86 Number of prevalent and incident ACs diagnosed per centre

Centre	No. of ACs	Prevalent	Incident
1	2	1 (50.0%)	1 (50.0%)
2	3	1 (33.3%)	2 (66.7%)
3	2	1 (50.0%)	1 (50.0%)
4	1	1 (100%)	0 (0%)
5	24	9 (37.5%)	15 (62.5%)
6	3	0 (0%)	3 (100%)
Total	35	13 (37.1%)	22 (62.9%)

13 (37.1%) of these were prevalent; ie. detected within 1 year of initial diagnosis of CLO. 22 (62.9%) were incident cancers; ie, diagnosed >1year after the initial diagnosis of CLO.

Of the 35 patients, 25 (71.4%) were picked up on true surveillance (documented surveillance endoscopies). 7 (20%) were diagnosed having had endoscopies for 'new symptoms' ('**N**') whilst on surveillance, and in the remaining 3 patients the indication for the endoscopy was unclear.

Of the true incident ACs (n=22), 13 (59.1%) were detected at specific surveillance endoscopies and 7 (31.2%) on endoscopies for 'new' symptoms.

Of the surveillance cohort, 23 (65.7%) died over the follow up period, of which 19 (out of 23) (82.6%) died with cause of death relating to AC (documented from death certificate information or as recorded in patient's notes) (including 1 in the close post-operative period). The cause of death in the other 4 was unclear from the notes.

Of the 23 that died 13 (48.3%) had undergone surgery for AC; 8 (34.8%) had received palliative treatment only (LASER or stenting), 1 (4.3%) snare excision and photocoagulation therapy and 1 (4.3%) neoadjuvant chemotherapy.

Of those patients *not* documented as being on surveillance programmes ('non-surveillance cohort'), 30 patients with adenocarcinoma were identified.

Survival analysis

Survival was calculated from histological diagnosis of AC to the last documented event in the notes if alive (censored), or to the point that the patient's death was recorded in the notes. Overall, 23 (65.7%) patients from the surveillance cohort died with a mean survival period of 1.38 years.

Kaplan-Meier survival tables were constructed for patients diagnosed with AC - having been grouped as shown below - and a cox regression analysis was performed.

1. All ACs from surveillance cohort (n=35)
2. All specific surveillance detected ACs (n=25)
3. ACs detected on endoscopy for 'new symptoms' whilst on surveillance (n=7)
4. ACs from non-surveillance cohort (n=30)
5. Prevalent ACs on surveillance (n=13)
6. Incident ACs on surveillance (n=22)

Of the 35 patients detected with AC who had been enrolled into a surveillance programme 12 (34.3%) had died by 1 year, 19 (54.3%) by 2 years and 22 (62.8%) had died by 5 years. Of the 30 patients detected with AC who had not been enrolled onto a surveillance programme, 14 (46.7%) had died by 1 year, 18 (60%) had died by 2 years and 19 (63.34%) by 5 years.

There were no significant differences found in survival times between these 2 groups (p=0.44 log rank) (p=0.445, cox regression) although a trend towards an increased survival was observed in those under surveillance, with the adjusted HR for surveillance programme AC found to be 0.94 (p=0.878, CI 0.44-2.03) (see Fig 38). When confounding variables are added to the cox regression model, smoking has some association with a decrease in survival (HR 1.2, CI 0.97-1.49) but age at

diagnosis, was found to be the only significant risk factor, with HR 1.04 (p=0.049; CI 1.00-1.08) (cox regression; p=0.072). On further analysis it was found that the age in the surveillance group was significantly older than the non-surveillance group (p=0.049, Indep T) (mean age in surv group = 70.0 years; mean age in non-surv = 63.1 years; p=0.049 on T test).

Unfortunately, data on associated patient co-morbidity was insufficient to allow adequate analysis in the cox regression model.

25 (71.4%) patients from the surveillance cohort had their AC detected on specifically documented surveillance endoscopies. 8 (32%) were dead by 1 year, 12 (48%) by 2 years and 15 (60%) by 5 years. On the cox regression model comparing survival with those whose cancers were detected on endoscopies performed for 'new symptoms' (N) there remained no significant differences (p=0.245) (see Fig 39).

22 incident ACs and 13 prevalent ACs were diagnosed whilst under surveillance. Their mortality figures are presented in Table 87 (see Fig 40) with no significant differences in survival on cox regression analysis (p=0.965).

Table 87 1,2 and 5 year mortality for patients diagnosed with AC

Cohort	**Number (n)**	**n dead by 1 year**	**n dead by 2 years**	**n dead by 5 years**
Surveillance (surv)	35	12 (34%)	19 (54%)	22 (63%)
Non-surveillance	30	14 (47%)	18 (60%)	19 (63%)
Specific surv ogd	25	8 (32%)	12 (48%)	15 (60%)
OGD for **N** on surv	7	3 (43%)	6 (86%)	6 (86%)
incident ACs on surv	22	7 (32%)	11 (50%)	12 (55%)
prevalent ACs on surv	13	5 (38%)	8 (62%)	10 (77%)

Figure 38 Kaplan Meier plot showing survival of patients with AC under surveillance vs ACs in rest of cohort

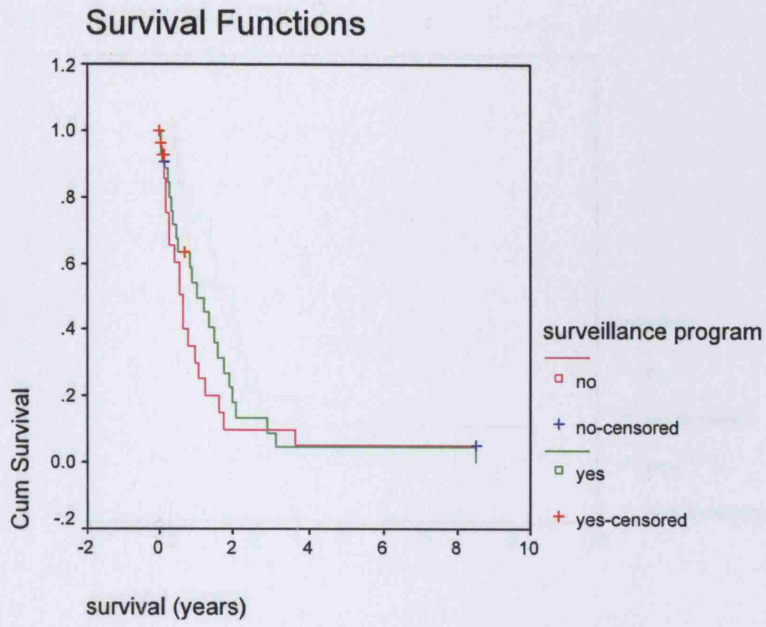


Figure 39 Kaplan Meier plot showing survival of patients with surveillance detected ACs vs ACs detected for 'new symptoms'

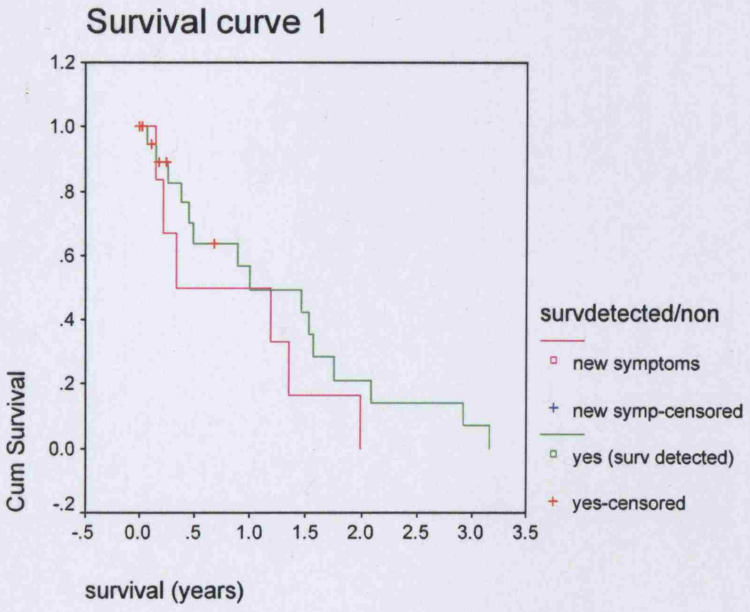
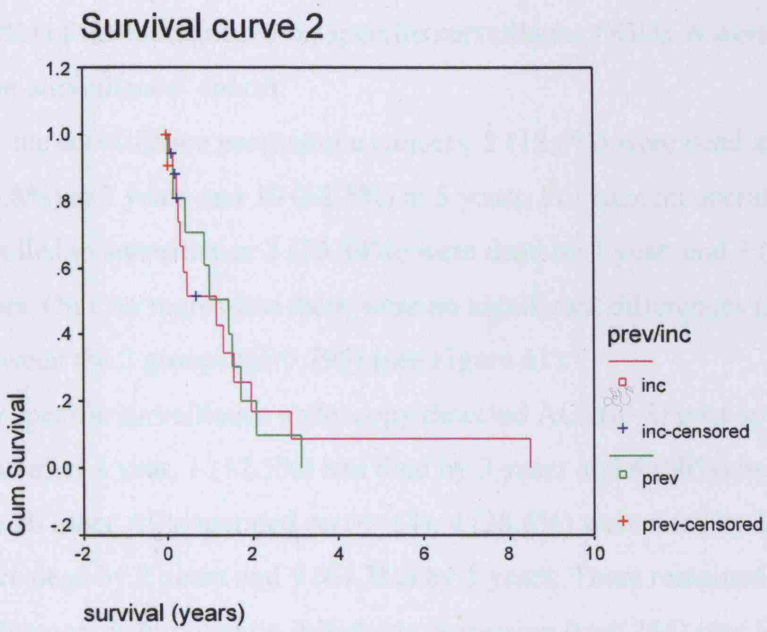


Figure 40 Kaplan M plot showing survival of patients with prevalent vs incident ACs diagnosed under surveillance



Survival after surgery for AC

A total of 22 (out of entire cohort) patients underwent surgery (oesophagectomy) for AC. 16 were diagnosed whilst enrolled on surveillance programmes with 8 (50%) of them diagnosed on specific surveillance OGDs. 6 were diagnosed in the 'non-surveillance' cohort.

For the surveillance programme cancers, 2 (12.5%) were dead at 1 year, 7 (43.8%) at 2 years and 10 (62.5%) at 5 years. For cancers operated on and not enrolled in surveillance 2 (33.34%) were dead by 1 year, and 3 (50%) by 2 and 5 years. On Cox regression there were no significant differences in survival between the 2 groups (p=0.795) (see Figure 41).

For specific surveillance endoscopy detected ACs (n=8) post-surgery, none were dead after 1 year, 1 (12.5%) had died by 2 years and 4 (50%) had died by 5 years. For all other ACs operated on (n=14), 4 (28.6%) were dead by 1 year, 9 (64.3%) were dead by 2 years and 9 (64.3%) by 5 years. There remained no significant differences in survival on initial cox regression (p=0.244) (see Figure 42).

In a cox regression model where the interaction term between surgery and surveillance was included, the ratio of the two hazard ratios is 0.696, indicating that the hazard for surgery for those on surveillance is 30% lower than for those having surgery not on surveillance. However, the confidence intervals were wide (CI 0.17-4.25).

Table 88 1,2 and 5 year mortality post-surgery for AC

cohort	number	N dead at 1 year	N dead at 2 years	N dead at 5 years
Surv programme AC	16	2 (12.5%)	7 (43.8%)	10 (62.5%)
Non-surv AC	6	2 (33.3%)	3 (50%)	3 (50%)
Specific surv-detected OGD AC	8	0 (0%)	1 (12.5%)	4 (50%)
Non surv-detected OGD AC	14	4 (28.6%)	9(64.3%)	9(64.3%)

Figure 41 Kaplan Meier plot showing survival in surveillance programme ACs vs non-surveillance programme ACs post oesophagectomy

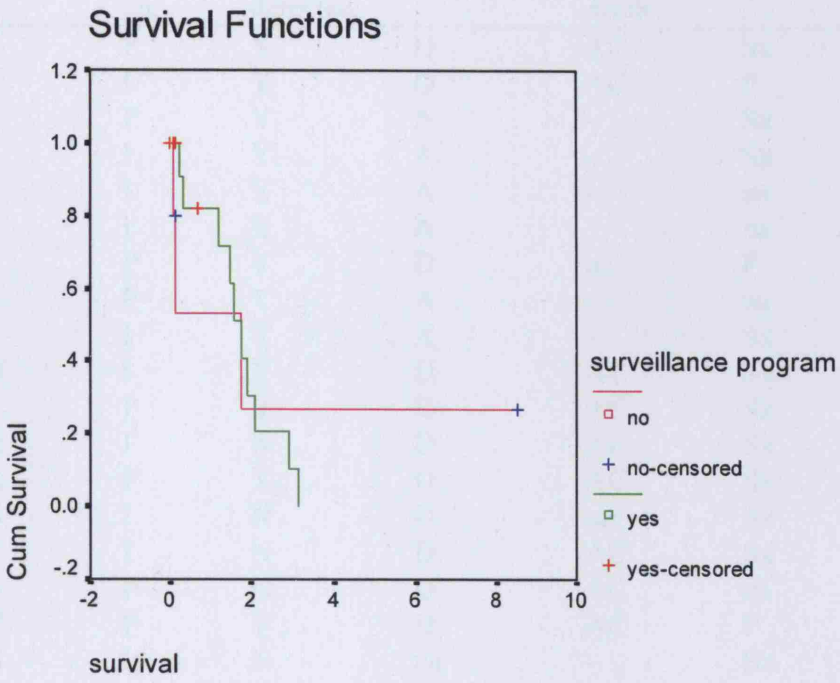


Figure 42 Kaplan Meier plot showing survival in specific surveillance-detected ACs vs non-surv-detected ACs post oesophagectomy

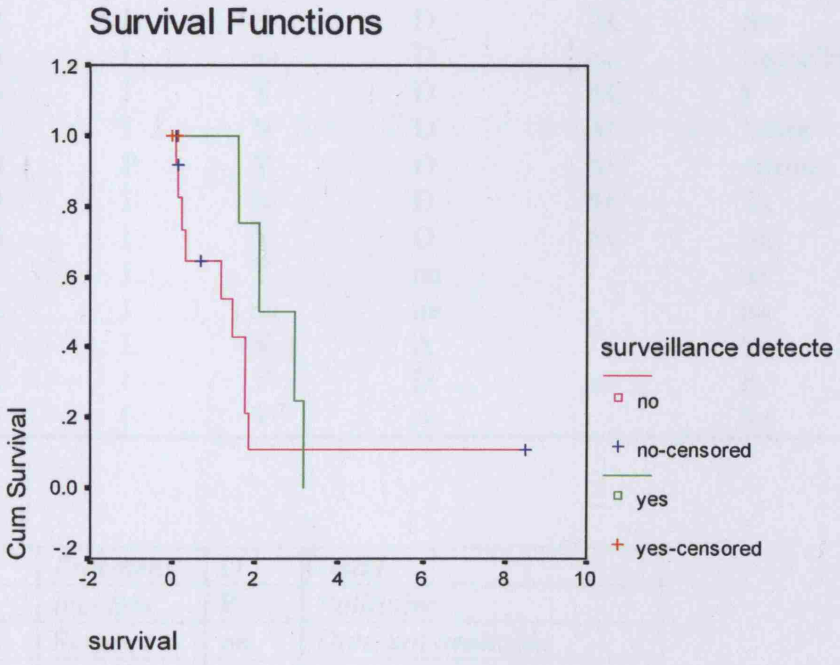


Table 89 AC data summary (from surveillance cohort)

Patient	Prev/ inc	Surv detected	Outcome	Cause death	Treatment	Survival (years)
1	P	Y	D	AC	Sx	2.08
2	I	Y	D	AC	P	0.38
3	P	Y	A	-	Sx	0
4	I	Y	A	-	Sx	0.14
5	I	Y	A	-	na	0.11
6	I	Y	A	-	na	0
7	P	Y	D	na	P	0.99
8	P	Y	A	-	na	0
9	I	Y	A	-	Sx	0.24
10	I	Y	D	AC	Sx	2.92
11	P	Y	D	AC	Sx	1.75
12	I	N	D	AC	Sx	0.14
13	P	Y	D	AC	Sx	1.45
14	I	N	D	na	Sx	0.33
15	I	N	D	AC	Sx	1.99
16	P	na	D	AC	na	0.02
17	P	Y	D	AC	P	0.89
18	I	N	na	-	Sx	-
19	P	Y	na	-	na	-
20	P	Y	D	AC	Sx	3.16
21	P	Y	D	Post-op	Sx	0.15
22	P	Y	D	AC	Sx	1.52
23	I	Y	D	AC	P	0.25
24	I	N	D	AC	Sx	1.18
25	I	na	D	na	Snare/Ptd	8.51
26	I	Y	D	AC	P	0.06
27	I	N	D	AC	Laser	1.34
28	P	Y	D	AC	chemo	0.44
29	I	N	D	AC	Sx	0.22
30	I	Y	D	AC	Sx	1.56
31	I	Y	na	-	na	-
32	I	na	na	-	na	-
33	I	Y	A	-	Sx	0.67
34	I	Y	D	na	P	0.48
35	I	Y	A	-	Sx	0

Key

P	*Prevalent*	D	*Dead*
I	*Incident*	P	*Palliative*
Sx	*Surgery*	na	*Data not available*
A	*Alive*	Ptd	*Photodynamic therapy*

Detection of dysplasia per endoscopic interval

Frequency of diagnosis of dysplasia (diagnosis ≥ 6) detected on certain endoscopic intervals was analysed.

Table 90a

Progression to dysplasia (≥6) on differing endoscopic intervals whilst on surveillance for various grades of disease

	Frequency of dysplasia detected per endoscopic interval											
Surv	*0-3m*		*3-6m*		*6-12m*		*12-18m*		*18-24m*		*24m+*	
diag	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
CLO (visual)	9	52	5	72	11	51	7	41	2	16	5	33
CLO (histo)	1	21	3	27	7	55	6	33	4	18	5	29
CLO (IM)	8	12	5	27	25	73	12	88	9	38	10	64
CLO (ID)	0	2	1	3	1	11	3	8	1	3	1	6
CLO (ID+IM)	0	1	2	3	5	20	8	16	3	5	5	7
LGD	4	7	5	21	4	51	0	33	1	15	1	13
HGD	6	7	1	4	1	5	0	3	-	-	-	-

On analysis comparing progression to worse disease per surveillance interval (A-F) (chi-square) the following p values were obtained for each disease subtype being surveyed (Table 94b):

Table 90b P values for chi-square analysis of data from Table 90a

Diagnosis	P value
1	P=0.482
2	P=0.756
3	**P=0.019**
4	P=0.819
5	P=0.712
6	**P=0.007**
7	P=0.299

There were no significant differences in frequency of diagnosis of dysplastic disease between various endoscopic intervals for surveillance of disease types 1,2,4,5 and 7. However, when surveillance is undertaken for CLO + IM and LGD, there is a significant difference in diagnosis of more dysplastic disease – LGD or worse, or HGD/AC respectively - depending on surveillance interval.
When diagnoses 1-5 are regrouped into 'non dysplastic CLO' and the analysis repeated then there are no longer any significant differences in detection of dysplasia between varying surveillance intervals (p=0.391). The actual mean endoscopic interval for surveillance of non-dysplastic CLO where dysplasia was detected was 1.41 years (SD 1.58; SE 0.123), compared to 1.26 years (SD 1.27; SE 0.04) where no dysplasia was detected; (p=0.183; indep T test). When analysed more closely (separate chi-square analysis comparing time interval A-F vs others) there is a significantly higher number of patients with worsening dysplastic disease detected at interval A (3 months or less) (p=0.013) whilst on surveillance for LGD.

Non-surveillance OGDs excluded:
When only disease detected at *specific* surveillance endoscopies were examined the results remained very similar, with significant differences in proportions of HGD/AC detected on varying endoscopic intervals for surveillance of LGD (p=0.007; chi-square), and no significant differences found for surveillance of all other grades of disease.

Table 91 Detection of dysplasia at varying endoscopic intervals per surveillance diagnosis (specific surveillance OGDs only)

	0-3m		*3-6m*		*6-12m*		*12-18m*		*18-24m*		*24m+*	
Surv diag	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
CLO (visual)	9	52	5	72	10	51	7	41	2	16	5	33
CLO (histo)	1	21	3	27	7	55	6	33	4	18	5	29
CLO (IM)	8	12	5	27	25	73	12	88	9	38	10	64
CLO (ID)	0	2	1	3	1	11	3	8	1	3	1	6
CLO (ID+IM)	0	1	2	3	5	20	8	16	3	5	5	7
LGD	4	7	5	21	4	51	0	33	1	15	1	13
HGD	6	7	1	4	1	5	0	3	0	0	0	0

Progression to specific grades of dysplasia

On examining progression to specific grades of dysplasia per surveillance interval, it was found that 42.9% (15/35) of the ACs were detected at surveillance intervals of 3 monthly or less (interval A) and 54.3% at intervals of 6 monthly or less (intervals A+B) (see Table 92):

Table 92 Progression to specific grades of disease on varying surveillance intervals

	worst disease				**Total**
Surveillance interval	non-dysp CLO	LGD	HGD	AC	
0-3m	102	8	5	15	130
3-6m	158	11	6	4	179
6-12m	266	43	5	6	320
12-18m	222	28	3	5	258
18-24m	95	18	1	1	115
24m+	152	23	0	4	179
Total	995	131	20	35	1181

Progression to dysplasia between centres

Table 93 shows frequency of progression of all endoscopic 'events' under surveillance to dysplasia (or worsening dysplasia) (diagnosis ≥ 6) in all 6 centres:

Table 93a Progression to dysplasia/worsening dysplasia between centres

		No	Yes	Total
Centre	1	65 (84.4%)	12 (15.6%)	77
	2	44 (71.0%)	18 (29.0%)	62
	3	53 (86.9%)	8 (13.1%)	61
	4	101 (79.5%)	26 (20.5%)	127
	5	503 (82.3%)	108 (17.7%)	611
	6	231 (93.5%)	16 (6.5%)	247
Total		997 (84.1%)	188 (15.9%)	1185

P<0.001 (chi-square)

On analysis there are significant differences in proportions of events progressing to dysplasia between the centres (p<0.001, chi-square).

When re-analysed examining surveillance of specific grades (non-dysplastic CLO, LGD and HGD separately) of disease the following tables are produced:

Table 93b Progression to dysplasia of non-dysplastic CLO:

		No	Yes	Total
Centre	1	45 (78.9%)	12 (21.1%)	57
	2	32 (65.3%)	17 (34.7%)	49
	3	49 (87.5%)	7 (12.5%)	56
	4	68 (73.1%)	25 (26.9%)	93
	5	418 (82.1%)	91 (17.9%)	509
	6	225 (94.5%)	13 (5.5%)	238
Total		837 (83.5%)	165 (16.5%)	1002

P<0.001 (chi-square)

Table 93c Progression to HGD/AC of LGD under surveillance

		N	Y	Total
Centre	1	19 (100%)	0 (0%)	19
	2	12 (92.3%)	1 (7.7%)	13
	4	32 (97.0%)	1 (3.0%)	33
	5	74 (87.1%)	11 (12.9%)	85
	6	4 (66.7%)	2 (33.3%)	6
Total		141 (90.4%)	15 (9.6%)	156

p=0.069 (chi-square)

Table 93d Progression to AC of HGD under surveillance

		N	Y	Total
Centre	1	1 (100%)	0 (0%)	1
	3	4 (80.0%)	1 (20.0%)	5
	4	1 (100%)	0 (0%)	1
	5	11 (64.7%)	6 (35.3%)	17
	6	2 (66.7%)	1 (33.3%)	3
Total		19 (70.4%)	8 (29.6%)	27

p=0.854 (chi-square)

For surveillance of non-dysplastic CLO, there are significant differences in proportions of endoscopic events progressing to dysplasia between the 6 centres ($p<0.001$, chi-square). Centres 2 and 5 appear to have significantly higher proportions progressing to dysplasia ($p=0.010$ and $p=0.002$ respectively on separate chi-square analysis) and center 6 significantly less ($p<0.001$, chi-square). There are no significant differences in frequency in detection of HGD/AC for patients being surveyed for LGD between the centers ($p=0.069$, chi-square) or in detection of AC for patients being surveyed for HGD ($p=0.854$, chi-square).

Surveillance biopsies

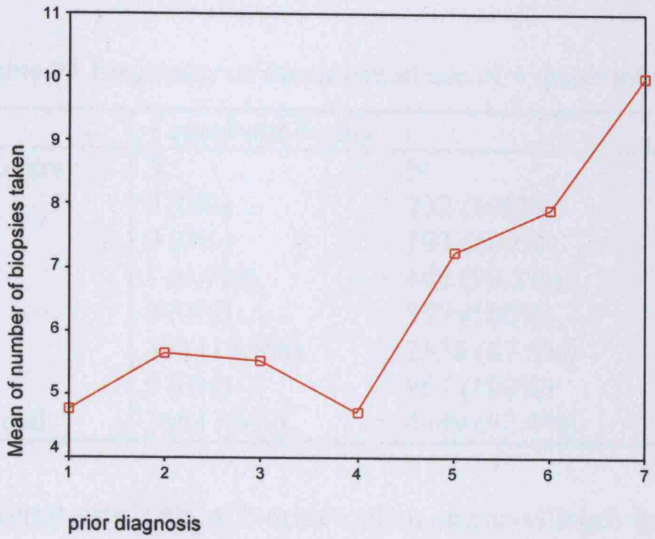
The mean number of biopsies taken on follow-up endoscopy, whilst on surveillance for specific diagnoses, were calculated. The results are presented in the Table 94:

Table 94 Mean number of surveillance biopsies taken per grade of disease

Surveillance diagnosis	Mean no. biopsies	N	STD	SE
CLO (visual)	4.76	238	3.94	0.255
CLO (histo)	5.64	101	4.50	0.447
CLO (IM)	5.54	127	3.46	0.307
CLO (ID)	4.72	18	4.00	0.942
CLO (ID+IM)	7.24	21	5.26	1.148
LGD	7.92	12	5.55	1.602
HGD	10.00	7	5.26	1.988
Total	5.36	524	4.13	0.181

There is a significant difference between the mean number of biopsies taken per surveillance diagnosis with a trend for more biopsies to be taken the more severe the disease being surveyed ($p<0.001$, one-way anova) (see Figure 43).

Fig 43 Means plot showing number of biopsies taken per grade of disease surveyed



Use of Four quadrant biopsy technique

The proportions of biopsies taken using a '4 quadrant technique' whilst on surveillance (per centre) are presented in Table 95 below (NB these include the first/diagnostic OGD).

Table 95 Frequency of documented use of 4 quadrant biopsy technique

	4 quadrant biopsy		
Centre	Y	N	Total
1	0 (0%)	232 (100%)	232
2	0 (0%)	193 (100%)	193
3	1 (0.7%)	142 (99.3%)	143
4	0 (0%)	377 (100%)	377
5	364 (12.5%)	2538 (87.5%)	2902
6	0 (0%)	967 (100%)	967
Total	365 (7.6%)	4449 (92.4%)	4814

Overall only 7.6% of biopsies taken on surveillance were documented as taken using this technique with only 1 centre regularly taking biopsies using this technique.

Factors affecting surveillance interval

The presence of strictures, ulcers or other associated upper GI disease such as duodenitis, duodenal ulceration, gastritis, gastric ulceration or oesophageal polyps were noted and the effect on endoscopic interval examined.

Table 96 Endoscopic interval and presence of oesophageal strictures

	Presence of strictures		
Endoscopic interval	Y	N	
0-3m	33 (25.4%)	97 (74.6%)	130
3-6m	33 (18.4%)	146 (81.6%)	179
6-12m	39 (12.2%)	281 (87.8%)	320
12-18m	35 (13.6%)	223 (86.4%)	258
18-24m	12 (10.4%)	103 (89.6%)	115
24m+	21 (11.7%)	158 (88.3%)	179
Total	173 (14.6%)	1008 (85.4%)	1181

There was a significant association between endoscopic interval and presence of oesophageal strictures at diagnosis ($p=0.002$, chi-square), with shorter intervals associated with a higher proportion of strictures present. Patients having endoscopies at intervals from 0-3 months (interval A) were significantly more likely to have had a stricture diagnosed previously ($p<0.001$, chi-square).

Table 97 Endoscopic interval and presence of oesophageal ulceration

	Presence of ulcers		
Endoscopic interval	Y	N	
0-3m	23 (17.7%)	107 (82.3%)	130
3-6m	31 (17.3%)	148 (82.7%)	179
6-12m	48 (15.0%)	272 (85.0%)	320
12-18m	28 (10.9%)	230 (89.1%)	258
18-24m	16 (13.9%)	99 (86.1%)	115
24m+	14 (7.8%)	165 (92.2%)	179
Total	160 (13.5%)	1021 (86.5%)	1181

There is a significant association between endoscopic interval and presence of oesophageal ulceration at diagnosis ($p=0.046$, chi-square) with intervals of 24

months + (interval F) less likely to be associated with the presence of ulcers (p=0.015, chi-square).

Associated Upper GI disease

On chi-square analysis, there were no significant differences between endoscopic interval and proportion of patients with associated upper GI disease – duodenitis (p=0.639); DU (p=0.287), gastritis (p=0.063), GU (p=0.494) and oesophageal polyps (p=0.738) (nor for gastric or duodenal polyps; p=0.671 and 0.564 respectively).

Table 98 Endoscopic interval and presence of associated upper GI disease

	duodenits		*DU*		*gastritis*		*GU*		*Oeso polyp*	
	Y	**N**	**Y**	**N**	**Y**	**N**	**Y**	**N**	**Y**	**N**
0-3m	12	118	3	127	6	124	7	123	1	129
3-6m	18	161	9	170	25	154	8	171	0	179
6-12m	29	291	17	303	34	286	8	312	2	318
12-18m	24	234	12	246	28	230	6	252	1	257
18-24m	14	101	1	114	19	96	4	111	1	114
24m+	11	168	6	173	21	158	8	171	0	179
total	108	1073	48	1133	133	1048	41	1140	5	1176

Multiple linear regression analysis

A multiple linear regression model was constructed for factors thought to have a possible effect on surveillance interval. The following equation was constructed:

Y=c+m1x+m2x+m3x +…..m8x

Y= dependent variable, outcome = surveillance interval

M = independent variable, predictor = age, grade of disease, presence of oesophageal strictures, presence of oesophageal ulcers, presence of duodenitis, presence of duodenal ulceration, presence of gastritis, presence of gastric ulceration.

Initial regression was done simultaneously:

The only significant independent variables were age which showed a negative association (Beta= -0.109, associated p value<0.001) (ie the older patients got the shorter the surveillance intervals) and grade of disease which also showed a negative association (Beta=-0.104, associated p value<0.001) (ie the worse the grade of disease the shorter the surveillance interval).

Table 99 SPSS Output table for simultaneous linear regression for factors affecting surveillance interval

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	2.488	.713		3.489	.001
	age	-1.06E-02	.003	-.109	-3.758	.000
	strictures	5.389E-02	.102	.015	.527	.598
	oeso ulcers	.169	.106	.046	1.587	.113
	NEWGRAD	-.298	.083	-.104	-3.585	.000
	duodenitis	.156	.128	.036	1.221	.222
	DU	-.172	.183	-.027	-.943	.346
	gastritis	-1.85E-02	.117	-.005	-.158	.875
	GU	-.309	.199	-.045	-1.556	.120

a. Dependent Variable: surv interval

Key

NEWGRAD	**Grade of disease**
DU	**Duodenal ulcer**
GU	**Gastric ulcer**

Stepwise regression showed similar results; as did forwards and backwards regression.

Management of HGD:

A total of 34 patients were diagnosed with HGD; 13 at the same time as their initial diagnosis of CLO was made and 21 on subsequent follow-up endoscopies. 14 (41.2%) developed cancer over the follow-up period; 7 within 1 year of their diagnosis of HGD (ie considered to be prevalent cancers).

'surgery patients' (n=14)

Of the 34 patients, 14 (41.2%) underwent surgery (oesophagectomy) at some time after diagnosis. 4 underwent surgery within 3 months of the diagnosis of HGD, 5 between 3 and 6 months, 3 between 6 and 12 months and 2 between 1 and 2 years. The overall mean time to surgery was 6.6 months.

6 of the 14 were documented to have had surgery either for a pre-operative diagnosis of AC or had subsequent post-operative histology confirming the presence of AC. 2 had post-operative histology demonstrating the presence of HGD only ('multi-focal' in one of the cases) and the histology was unclear from the notes in the remaining 6.

11 (32.4%) patients, from 3 of the centres, underwent surgery for a pre-operative diagnosis of HGD only (no evidence of a pre-operative diagnosis of AC). 7 of them had a confirmatory OGD and biopsy within 3 months, and all but 2 underwent surgery (oesophagectomy) within 6 months of their diagnosis. 4 (36.4%) had AC on post-operative histology.

'surveillance group' (n=17)

17 (50.0%) patients underwent a period of true 'surveillance' (from all of the centres). Patients that only had a 'confirmatory' OGD within 1 month of their initial diagnosis of HGD or had a repeat OGD and referral to surgery within 6 months were not included in the surveillance cohort.

8 of them (47.1%) developed AC over the surveillance period.

The mean number of endoscopies performed after diagnosis of HGD was 3.59 (4) with an overall mean surveillance interval of 0.718 years (8.62 months) (range – 0.12-1.17 years). 3 patients died over the follow-up period 1.29, 3.83 and 3.2

years after being diagnosed with HGD. All 3 had been diagnosed with AC; 1 having had surgery (survival 3.06 years post surgery), 1 having had PDT and the other just palliative care.

Of the patients that survived, 11/15 (73%) had survived > 1 year (of which 5/15 (33%) had survived > 2 years) at documentation of their last follow-up record (mean overall survival period = (need to include LP0123) years). 3 had documentation of survival at less then one year post diagnosis and in one the survival figures were unclear.

'Photodynamic therapy (PDT) & LASER group' (n=6)

5 patients in total received PDT as their only treatment and one patient received LASER therapy.

In 4/5 (80%) of the patients treated with PDT, no documentation of a diagnosis of AC was evident.

1/5 (60%) patients treated with PDT died after a mean period of 3.2 years post diagnosis of their HGD; (AC documented as cause of death, but no documentation of AC pickup before this). 3/5 (60%) were documented to be alive at 0.27, 6.44 and 5.4 years post diagnosis. In 1 the outcome was unclear.

In the 1 patient that received LASER therapy, they went on to have surgery shortly after with a post-operative diagnosis of HGD on histology only. The outcome was unclear from the notes.

(4 patients had a diagnosis of AC made within 1 month of their diagnosis of HGD; 5 had no evidence of any further endoscopies documented.)

Survival analysis

A survival analysis was undertaken looking at patients who had undergone surgery for a pre-operative diagnosis of HGD only (n=11) vs patients that were surveyed and only had surgery when AC was diagnosed (n=16).

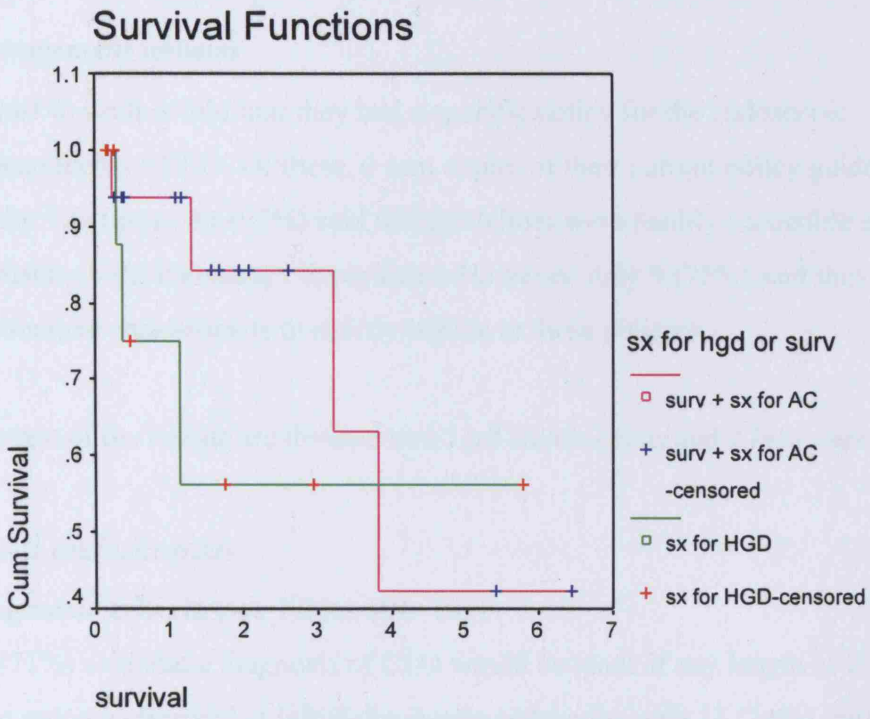
Of the 11 patients undergoing surgery for a pre-operative diagnosis of HGD, 2 (18%) were dead after 1 year and 3 (27%) were dead after 2 and 5 years. Of the 17 patients who were surveyed 1 (5.8%) was dead after 1 year, 2 (11.8%) were dead after 2 years and 4 (23.5%) were dead after 5 years.

The mean survival (for those that died) of patients in the surgery group was 3.55 years (SE 1.00; 95% CI 1.59-5.52) and 4.34 years (SE 0.75; 95% CI 2.86-5.81) in the surveillance group (p=0.401, cox regression) (see Figure 44).

Table 100 Mortality rates comparing surveillance vs surgery for HGD

cohort	**number**	**N dead at 1 year**	**N dead at 2 years**	**N dead at 5 years**
Surgery for HGD	11	2 (18%)	3 (27%)	3 (27%)
Surveillance for HGD	17	1 (5.8%)	2 (11.8%)	4 (23.5%)

Figure 44 Kaplan Meier plot showing survival in patients under surveillance vs surgery for HGD



Endoscopist survey/Questionnaire chapter

102 questionnaires were sent. A total of 45 (44%) replied. The response rate from the lead endoscopists of the centres was higher with 30/41 (73%) replying.

Management policies

12 (40%) centres said that they had a specific policy for the endoscopic management of CLO. Of these, 6 sent copies of their current policy guidelines. Of the 12 centres, 11 (92%) said that guidelines were readily accessible and available in the endoscopy department. However, only 9 (75%) said they encouraged endoscopists to strictly adhere to these policies.

The rest of the results are divided into 1.*all endoscopists* and 2.*lead endoscopists*.

1) *All endoscopists*

Diagnostic criteria (see Tables 101- 103)

32 (71%) said that a diagnosis of CLO would be made if any length of Barrett's type mucosa observed at initial diagnostic endoscopy with 11 (24%) stating that a minimum length was required – 6 (13%) requiring >3cm in order to make a diagnosis; 3 (7%) requiring >2cm and 2 (4%) requiring >1cm. 32 (71%) endoscopists did not require circumferential disease in order to make a diagnosis and recognised areas of non-confluent disease as CLO.

35 (78%) documented the precise level of the GOJ at diagnosis, 36 (80%) the SCJ and 25 (56%) mentioned the level of the diaphragmatic hiatus. 43 (96%) documented the length of CLO observed and 24 (53%) the proximal extent of non-confluent CLO if present.

If associated oesophagitis was present then 43 (96%) would document this with 16 (36%) noting the level of its proximal extent. Grading systems for oesophagitis varied with 14 (31%) using the 'LA' system, 7 (16%) the 'Savary-Miller', 3 (7%) a simple '1-4' system and 3 (7%) the system associated with 'endoscribe'.

Strictures, hiatus herniae, gastritis and duodenitis were noted if present by 44 (98%), 43 (96%), 34 (76%) and 34 (76%) of endoscopists respectively.
33 (73%) endoscopists biopsied all patients at first diagnostic endoscopy with 8 (18%) biopsying more than half and 3 (7%) less than half of all patients. 32 (71%) took 4 ('quadrantic') biopsies per level and 3 (7%) less than 4. 35 (78%) used standard biopsy forceps with only 1 admitting to using jumbo-sized forceps. The majority – 31 (69%) - took biopsies at 2cm intervals with 4 (9%) taking them at 1cm intervals and 1 at 3cm.
On the histology request form, 28 (62%) documented the level of the biopsy, 15 (33%) the GOJ and 19 (42%) the presence of hiatus herniae.
19 (42%) said that they tested all patients with CLO for *H Pylori* routinely, with 24 (53%) only testing in the presence of associated gastro-duodenal inflammation or ulceration. The majority of endoscopists – 25 (56%) - performed a Clo test alone as their preferred method of HP detection, with 7 (16%) opting for a combination of Clo and histology. The remaining endoscopists used varying combinations of Clo, breath test, serology and histology.
24 (53%) of endoscopists felt that they had changed their practice over the last 5-10 years; 13 (29%) in the recognition of the CLO segment itself, 11 (24%) in the length of CLO required in order to make a diagnosis and 19 (42%) in their biopsy technique.

Table 101

Diagnosed as CLO	Percentage of endoscopists
Any length columnarisation	71%
Min. length required	24%
>3cm columnarisation required	13%
Non-confluent disease	71%

Table 102

Documentation at endoscopy	Percentage of endoscopists
Length CLO	96%
Prox extent of non-confluent CLO	53%
GOJ	78%
SCJ	80%
Diaphragmatic hiatus	56%
Oesophagitis	96%
Prox extent oesophagitis	36%
Strictures	98%
HH	96%
Gastritis	76%
Duodenitis	76%

Table 103

Biopsy protocol	Diagnostic	Surveillance
4 quadrant	71%	71%
Standard forceps	78%	69%
2cm intervals	69%	67%

Surveillance

41 (91%) endoscopists stated that they surveyed CLO patients. Of those that surveyed 36 (88%) adopted a selective surveillance policy. 12 (29%) only surveyed patients with histological evidence of CLO and 21 (51%) required the presence of IM in order for the patient to be entered into a surveillance programme. Other documented requirements for surveillance included 'high risk patients' (n=1); more than 3cm of columnarisation (n=1); at least 8cm of columnarisation (n=1); the presence of dysplasia, ulcers or strictures (n=1); an ASA grade of 1-3 (n=1); and non-specified age/fitness requirements (n=1).
For surveillance biopsies, 31 (69%) used standard biopsy forceps, 3 (7%) jumbo forceps and 3 (7%) other, non-specified, types. 32 (71%) took 4 biopsies per level, 6 (13%) took 2 or less. 30 (67%) took biopsies every 2cm of columnarisation, 5 (11%) took them 1cm apart and 1 every 2-3cm.

Endoscopists varied in their selected surveillance intervals for specific grades of disease (see Table 104). Of those that undertook surveillance, the most frequent surveillance interval for uncomplicated disease was between 1 and 3 yearly. Surveillance for LGD was most commonly performed between 1-6 monthly (46%) (although 39% surveyed between 6 and 12 monthly). Surveillance for HGD was also most commonly performed at an interval between 1 and 6 monthly (51%), however, many (44%) surveyed more frequently than this.

5 (11%) of endoscopists stated that a direct referral to surgery would be considered if a diagnosis of HGD had been made.

6 (13%) endoscopists felt that it was reasonable to stop surveillance for 'stable' disease* – 2 after 5 years, 2 after 10 years and 1 after 1 year (in 1 no time was specified). 40 (89%) felt that other factors such as age and patient co-morbidity were reasonable indications to consider cessation of surveillance and 30 (67%) felt that if the patient was not a candidate for potential oesophagectomy then there was no benefit in continued surveillance.

Table 104 Surveillance interval for specific grades of disease (and as % of those that surveyed)

	Number (%) of endoscopists surveying at set intervals					
Diagnosis	<1m	1-6m	6-12m	1-3y	5y+	Total
CLO (visual)	0 (0%)	2 (5%)	2 (5%)	11 (27%)	0 (0%)	15 (37%)
CLO (histo)	0 (0%)	0 (0%)	0 (0%)	19 (46%)	1 (2%)	20 (49%)
CLO (IM)	0 (0%)	0 (0%)	4 (10%)	32 (78%)	2 (5%)	38 (93%)
CLO (ID)	1 (2%)	14 (34%)	17 (41%)	9 (22%)	0 (0%)	41 (100%)
LGD	0 (0%)	19 (46%)	16 (39%)	6 (15%)	0 (0%)	41 (100%)
HGD	18 (44%)	21 (51%)	1 (2%)	0 (0%)	0 (0%)	40 (98%)

* defined as 'no worsening histology, no increase in segment length and no deterioration in symptoms...' in the questionnaire

2) *Lead endoscopist (centres) survey results:*

Diagnostic criteria

25 centres (83%) said that a diagnosis of CLO would be made if *any* length of Barrett's type mucosa was observed at initial diagnostic endoscopy with 4 (13%) centres stating that a diagnosis would only be made if greater than 3cm of CLO seen (1 centre required the presence of >1cm of disease). 21 (70%) centres would make a diagnosis in the presence of only non-confluent areas of CLO mucosa, including streaks and isolated mucosal islands. Measurements at endoscopy for the gastro-oesophageal junction (GOJ) and squamo-columnar junction (SCJ) were recorded routinely in 24 (80%) and 25 (83%) centres respectively, however, only 19 (63%) centres stated the level of the diaphragmatic hiatus. All centres said that a measurement for length of CLO was always stated, and the proximal extent of non-confluent CLO (when recognised) was noted in 18 (86%) centres.

The presence of oesophagitis was stated, if present, in all centres, although, proximal extent was only noted routinely in 13 (43%) centres.

Classification for grading of oesophagitis varied with the *Los Angeles* system used in 11 (37%) centres, *Savary-Miller* in 5 (17%), *endoscibe* or *'1-4'* in 5 (17%) centres and no specific scoring system in the others (9).

Strictures, hiatus herniae, gastritis and duodenitis were noted if present in 30 (100%), 29 (97%), 24 (80%) and 25 (83%) centres.

23 (77%) of the centres stated that they would biopsy all patients with CLO at first diagnostic endoscopy. 5 (17%) centres stated that they felt they biopsied, on average, more than half the patients and 2 (7%) centres less than half.

22 (73%) of the centres said that they took four-quadrant biopsies at diagnostic endoscopy with 23 (77%) using 'standard' or 'normal' size biopsy forceps. Only 1 centre stated that they used jumbo-sized forceps.

The majority of centres, 22 (73%), stated that they took biopsies at 2cm intervals or less throughout the length of the CLO segment.

On the histology request form 19 (63%) centres stated biopsy site, 12 (40%) stated level of the GOJ and 13 (43%) stated whether a hiatus hernia was present.

14 (47%) centres said that they tested *all* patients with CLO routinely for *H Pylori* infection, with the other 16 (53%) only testing in the presence of associated gastro-duodenal inflammation or ulceration. 60% (18) performed a *Clo* test alone as their preferred method of detection, with 27% (8) opting for a combination of *Clo* in conjunction with histology or serology.

Table 105 Criteria for diagnosis of CLO (lead endoscopists)

Diagnosed as CLO	Number of centres
Any length columnarisation	25 (83%)
Only if ≥ 3cm columnarisation	4 (13%)
Non-confluent columnarisation	21 (70%)

*1 centre required >1cm to be visualized

Table 106 Documentation at endoscopy – lead endoscopist

Observations noted at endoscopy	Number of centres
Length CLO	30 (100%)
Proximal extent non-confluent CLO	18 (60%)
Level of GOJ	24 (80%)
Level of SCJ	25 (83%)
Level of diaphragmatic hiatus	19 (63%)
Oesophagitis	30 (100%)
Prox extent oesophagitis	13 (43%)
Hiatus hernia	29 (97%)
Gastritis	24 (80%)
Duodenitis	25 (83%)
Strictures	30 (100%)

Table 107 Biopsy protocol –lead endoscopists

Biopsy technique	diagnostic	Surveillance
Standard sized forceps	23 (77%)	20 (67%)
Jumbo-sized forceps	1 (3%)	2 (7%)
4 quadrant biopsies	22 (73%)	22 (73%)
2cm intervals	22 (73%)	20 (67%)

Surveillance

27 (90%) centres surveyed patients with CLO. Of those that surveyed, 5 (19%) surveyed *all* patients with CLO routinely, with 16 (59%) surveying greater than half (6 (22%) surveyed less than half). 9 (33%) centres surveyed CLO without histological confirmation, and 14 (52%) surveyed disease with confirmatory CLO on histology but no evidence of IM.

Surveillance intervals for each grade of disease are presented in the table below:

Table 108 Number of centres surveying at set intervals (and as percentage of those surveying)

	Number (%) of centres surveying at set intervals				
Diagnosis	<1m	1-6m	6-12m	1-3y	5y+
CLO (visual)	0 (0%)	2 (7%)	0 (0%)	7 (26%)	0 (0%)
CLO (histo)	0 (0%)	0 (0%)	0 (0%)	13 (48%)	1 (4%)
CLO (IM)	0 (0%)	0 (0%)	1 (4%)	23 (85%)	2 (7%)
CLO (ID)	1 (4%)	12 (44%)	9 (33%)	6 (22%)	0 (0%)
LGD	0 (0%)	15 (56%)	9 (33%)	4 (15%)	0 (0%)
HGD	11 (41%)	14 (52%)	1 (4%)	0 (0%)	0 (0%)

Of those surveying, 13 (48%) surveyed non-dysplastic CLO (confirmed histologically) at 1-3 yearly intervals with 23 (85%) surveying CLO with IM on histology at this interval. 15 (56%) centres surveyed LGD at 1-6 monthly intervals.

25 (93%) centres adopted a frequent surveillance policy for HGD, repeating the endoscopy at 6 monthly or less intervals. 2 (7%) centres made a direct referral for surgery if HGD was detected and 1 centre stated that they would repeat the biopsy and ask for a second specialist pathologist opinion.

Of those surveying, 20 (74%) centres used standard size forceps for surveillance biopsies with only 2 (7%) using jumbo forceps routinely.

22 (81%) centres admitted to taking 4 biopsies per level with 20 (74%) biopsying every 2cm and 3 (11%) every cm.
4 (15%) centres felt that 'stable disease' over a follow-up period of 5 years or more was a reasonable indication to stop surveillance. All the centres that surveyed, however, felt that age and co-morbidity were justifiable reasons to stop surveying and 19 (70%) would stop if the patient was assessed as not being fit enough to undergo an oesophagectomy if future cancer detected.

Change in practice

60% of endoscopists felt that they had changed their approach to the management of CLO in the last 5-10 years. 61% of them said that this was in the recognition of the columnar-lined segment itself; 56% felt that their definition of CLO had changed based on length recognised and 78% said that they had altered their biopsy technique.

Validity of data (Criticisms/shortfalls of the methodology)

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Collection of data

There is a potential for errors in initial registration of patient data. Firstly, it is possible that an incorrect diagnosis may have been made, either at the endoscopic or histopathological interpretation stage (*see Introduction; Diagnostic Criteria – Histological diagnosis of CLO + dysplasia*); secondly, it is possible that, due to human error, incorrect patient details or diagnostic information may have been entered.

These errors may be picked up at a later stage when further data on that patient are checked prior to entry onto the database (eg updated endoscopy reports).

It is possible, therefore, that for analyses done on basic demographic information obtained purely from form 1s (ie before completion of stage 2) then errors at this stage may affect results. Data analysed after form 2 completion, however, is less likely to show these persisting errors. Information at this stage is often based on a larger number of endoscopies and histological examinations done over a number of years and likely to have been corroborated by at least 2 people by this time. (NB all data used for analyses in this study had come from information entered at the form 2 stage).

Transference of data from the notes may also be subject to human error, and may be subject to some degree of variation in interpretation at the time.

Inputting of data

Data may be entered incorrectly onto the database; either due to human error or due to subjectivity of interpretation of various pieces of information.

Design of study and analysis of data

By definition, all patients registered with UKBOR have a diagnosis of CLO. There is, therefore, no '*non CLO*' control group to compare these patients with. Subjective comparisons can be made with characteristics known of the 'general population' and the presence of frequently occurring traits in the Barrett's population may be assumed to be more prevalent or even be regarded as 'risk

factors' for development of the disease; however, it impossible to make any accurate conclusions without the capacity for direct analytical comparison.
For the majority of analyses, therefore, it was risk factors for the development of dysplastic disease in an established columnarised oesophagus that we were examining.

Once a patient is registered, data are collected prospectively for that patient - endoscopy and histology reports are sent to the registry and the database updated. Data analysis, however, is retrospective, with patients grouped by outcome (usually dysplasia or no dysplasia) and independent variables examined amongst these various groups (*see Patients and Methods; statistical methods/analysis chapter*).
There are a number of criticisms of this type of analysis.

Calculation of risk
We were particularly interested in examining various patient risk factors for the development/progression of dysplastic disease in CLO, and calculation of an *Odds Ratio* was used in a number of analyses.
Relative risk is normally applied to prospective data analysis, where patients are sampled by the characteristic (risk factor) of interest and it is possible to calculate incidence rates directly. With retrospective (*case control*) studies the patients with and without the disease are sampled and the presence or absence of risk factors are analysed; however, the odds ratio can give a good approximation of the relative risk, particularly if the incidence of the disease is low.
Estimation of relative risk from case-control studies can be done assuming the following equation based on the table below (*see p.75 Patients and Methods; Statistical methods/analysis*) (271):

Exposed to risk factor	Group by outcome (eg dysplasia)	
	Cases	Controls
Yes	*a*	*b*
No	*c*	*d*

$$\text{Relative risk} = \frac{a/(a+b)}{c/(c+d)}$$

$$\frac{a/(a+b)}{c/(c+d)} = \frac{a(c+d)}{c(a+b)}$$

When the disease relatively uncommon, **c** is negligible in relation to **d** (the number of people who aren't exposed to the risk factor but who have the disease is small compared to those who haven't been exposed and don't have the disease) and, *in the population*, **a** is negligible compared to **b** (those with the risk factor who have the disease is still small compared to those exposed who don't have the disease).
Therefore:

$$\frac{a(c+d)}{c(a+b)} \quad \text{reduces to} \quad OR = \frac{ad}{bc}$$

Hence, odds ratio can be calculated as an estimation of relative risk.

Confounding variables
There is potential for confounding variables in retrospective case control studies. In prospective analyses it is easier to match groups accordingly prior to analysis in order to reduce the chance of confounders having an influence on the final result and this may be done to a certain extent for retrospective analyses. One obvious drawback of matching, however, is that once the groups are matched for a particular factor, then conclusions about relationships with outcome and this factor cannot be drawn.
Statistical tests such as multiple linear regression, multiple logistic regression and cox regression – all used in this study - examine for confounding variables and some authors argue that this gives a more useful result than the outcome obtained from matched analyses.

For some of the studies, where the above statistical tests were not used, cohorts were directly compared for named confounding variables and statistical analyses done on frequency of these factors occurring between groups.
The most common confounding variables - known from prior studies where the dependent variable was also adenocarcinoma or dysplasia – namely age, smoking habits and gender, were incorporated into the majority of analyses.

Missing data

For a number of analyses data entry was incomplete. When this occurred, these patients were *not* included in the analysis and SPSS dealt with them by listwise deletion.
The assumption was that these data were missing completely at random and that their removal did not, therefore, bias the overall outcome.
It is recognised that this is an assumption and that for some of the sub-analyses so called 'non-ignorable missingness' could exist.
For example, on analysis of patient's weight it may be that patients were more likely to have their weight documented if they were considered to be 'overweight'.
One way to deal with this can be to input data for the missing values based on other research/experimental results – so called *'means substitution'* - (for example mean weight of patients with CLO from other research studies) and perform the analysis with the now 'complete' data set; however, this method has gone out of favour (275). Other methods of dealing with missing data such as *Maximum Likelihood Estimation* (MLE), *Approximate Bayesian Bootstrap* (ABB) (using logistic regression to estimate probability of response/non-response on the dependent variable y, based on covariates Xi) and *Multiple Imputation* (MI) (method of generating multiple simulated values for each incomplete datum, then iteratively analyzing datasets with each simulated value substituted in turn) have all been advocated and there are pros and cons for each method; the details of which are considered beyond the remit of this thesis (276) (277).

Discussion

Patient characteristics

Age

The mean age of the entire cohort at diagnosis was 62.7 years and was similar to other European studies (131) (278) (133), with men being diagnosed significantly younger (60.39 years) than women (66.4 years) (p=0.000, Indep t). The mean age at diagnosis of AC (men and women combined) on initial diagnostic (for CLO) endoscopy was 66 years and on worst disease endpoint was 70.82 years.
Overall, men and women combined, patients diagnosed with non-dysplastic disease at initial diagnoses were significantly younger than those diagnosed with dysplastic disease (p=0.0027; indep T).
There was a trend for age of patients at diagnosis of CLO (ΔCLO) (all grades combined) to increase over time; although this did not reach statistical significance (p=0.091, linear regression); and is not reflected in more recent studies done at UKBOR on greater numbers of patients which shows a trend in the other direction (279).

Disease proportion

The proportion of overall dysplastic disease at diagnostic endoscopy was 9.9%; with LGD making up 6.5%, HGD 1.1% and AC 2.3%. As their worst disease endpoint, 22.8% of patients had a diagnosis of dysplastic disease; with LGD making up 15.7%, HGD 2.0% and AC 5.1%. Incidence rates for the development of HGD/AC in CLO, although not calculated for this study specifically*, have been published by UKBOR at 0.62% per year (280) and are similar to other data published in the U.K. and USA with an annual incidence quoted as being between 0.7 and 1.3% (281) (282).
There was a large number of prevalent cancers (62% of all the cancers), of which 73% (30/41) were diagnosed on the patient's first *diagnostic (for CLO)* endoscopy. This is a worryingly high proportion of the cancers and reflects a

* Incidence data on the natural history of CLO was a specific remit for other UKBOR researchers at the time

group of patients with a particularly poor prognosis. Only 25 (2.0% of all patients in the study) developed true incident AC.

Gender

The overall male:female ratio for all disease subtypes was 1.65:1 which is similar to other recently published data (283) (284) with the proportions of males increasing significantly with increasing severity of dysplastic disease. For AC, the male:female ratio at initial diagnosis was 4:1; at worst disease endpoint, the ratio was 2.47:1. The reason for the preponderance of males is unclear. Authors have suggested that premenopausal women may be protected to some degree from the development of CLO due to hormonal factors (135) although evidence to support this is limited. Interestingly in this study it was gender ratio for *prevalent* HGD/AC that was significantly weighted towards males when compared to non-HGD/AC and *incident* HGD/AC – although still much more common in males - did not show such a striking gender difference. This may possibly be a reflection in timing of presentation. Males may tend to delay presenting until a later stage in the disease (ie. until pre-existing but undetected cancer is present) and women may be presenting, in general, at an earlier stage. Whether this could be translated into a reflection of symptom thresholds, or varying health attitudes between men and women is debatable (and likely controversial!).

Weight

The frequency of documentation of weight in the patient records was fairly low (14.3-32.5%) and it was apparent that certain centres tended to document weight more often than others. Whether there is an inherent bias to document the weight of patients that are generally more overweight (or perhaps the opposite) is debatable.

Body mass index (BMI) (calculated as weight (Kg)/height $(m)^2$) has been widely used as an indication of obesity and currently categorises people as in the following table:

BMI	≤20	Underweight
BMI	20-25	Desirable
BMI	25-30	Overweight
BMI	≥ 30	Obese
BMI	>35	Morbidly obese

In 1999, national surveys (274) showed that 60% of all men were overweight or obese and 70% of men over the age of 45 fell into one of these two categories. This proportion had increased since the previous study done in 1993 with an extra 6% of the male population now falling into the obese category (19% vs 13%). Proportions of men who are overweight have exceeded proportions of women in the same category with nearly half of men considered overweight in 2001 compared to a third of all women.

There have been a number of recent studies which have shown that obesity has significant implications on development of CLO and AC (285) (286) with a recent study by de Jonge et al (287) suggesting that early obesity (<20 years of age) may be significantly related to development of AC in later life.

In our study, the mean weight for all patients with uncomplicated CLO was 74.86 kg, (males, 79.32 kg and females, 67.76 kg). Unfortunately, documentation of height in medical records was so infrequent that it was difficult to generate accurate data on BMI; however, permitting the assumption that the average height of our cohort was similar to the general population in the UK - 1.76m for males and 1.62m for females (274) - allowed generation of estimated BMIs and subsequent analysis to be performed. Previous data published from the Registry has suggested that obesity may be a risk factor for the development of CLO in men under the age of 50 (288), and we therefore categorized patients into those below and above this age. Although not quite reaching statistical significance, this showed a striking preponderance of dysplastic disease in obese males under the age of 50 with an associated odds ratio of 7.27 compared to non-obese patients. The risk of a high BMI in all other groups did not show such a trend.

If there is a genuine significant risk of progression of GORD through dysplasia in obese patients – particularly younger males - then the above national survey

figures suggest a worrying trend, supported by the progressive increase in incidence of AC in the U.K.

Blood group

Only 29.6% of patients had documentation of their blood group in their medical records.

However, of the patients analysed, those who were O Rhesus negative appeared to have a significantly higher proportion of HGD/AC compared to non HGD/AC ($p=0.001$, chi-square). Few studies have examined blood group and development of CLO, however a recent unpublished study by UKBOR has suggested that patients who are O negative may have a higher incidence of CLO than expected (Caygill et al, personal communication).

Smoking

Smoking as a risk factor for the development of CLO is controversial, however a number of studies have demonstrated an increased risk of development of dysplastic disease and AC amongst smokers with established CLO (139) (289). From our cohort, documented evidence of smoking habits were present in 75.9% of all patients. The prevalence of smokers in the cohort was fairly high at 54.3%, with exactly half of them current and half ex-smokers. Although it is impossible without a control group to comment on whether the high proportions of smokers in the cohort was linked to their initial Barrett's disease, it does seem striking that this is almost twice as high as the normal population, with data on prevalence of smokers in the UK as a whole suggesting figures of 28% (in people over the age of 16 years) between 1998 and 1999, and 25% in the years 2004/5 (274).

In our study any history of smoking was significantly associated with the development of HGD/AC when compared to non-smokers, with smokers 2.8 times more likely to have severely dysplastic disease (HGD or worse) ($p<0.001$). Ex-smokers appeared to remain at a significant high risk of HGD or AC and there appeared to be no reduction in risk in those that had given up for 10 years or more (in fact the OR for this group was actually higher - OR 3.24 vs 2.17).

There was no significant difference in development of HGD/AC when current smokers were compared to ex-smokers (p=0.777).
One study has shown a dose-dependant risk of AC development with smoking (140) – however, our study did not support this. In fact, current smokers who smoked 20 a day or more did not appear to be at a significantly higher risk of developing dysplastic disease than those who smoked less than 20 a day (p=0.577, chi-square). (Interestingly the odds ratio for those who smoked less than 20 a day compared to non smokers was higher (3.42) than those who smoked 20+ a day compared to non-smokers (2.73)).

When the cohort was divided into males and females, however, the results were strikingly different. Although it appeared that there was a trend for female smokers to have higher proportions of dysplastic disease (OR 1.75) there were no significant differences compared to non-smokers on statistical analysis of any of the categories. In males, however, the findings were similar to that of the cohort as a whole, with smoking at any time significantly associated with higher proportions of severely dysplastic disease and ex-smokers at similar risk to current smokers.
Why smoking should be a risk factor for the development of more severe disease in men but not in women is hard to explain, but some authors have postulated that female hormones such as oestrogen may play a role, with overall protective effects on oesophageal disease progression.

Alcohol

The effects of alcohol on the development and progression of reflux-induced oesophageal disease is less well described. Recent studies, however, have suggested that increased alcohol consumption may be linked with the development of GORD and CLO (290) (291).
From our study alcohol usage was fairly well documented with 71.4% of patients having a record of alcohol consumption frequency in their notes. The alcohol

'score' used was similar to the above smoking score in that it was the one documented nearest to the initial diagnostic OGD.
On analysis there were no significant differences in alcohol usage and severity of all grades of disease (p=0.384) nor on proportions of HGD/AC (p=0.650); and there remained no significant differences when the cohort was sub-divided into males and females and analysed separately.

Co-morbidity

There were relatively high proportions of patients with associated orthopaedic/rhematological disease (18.3%), ischaemic heart disease (14.4%), hypertension (15.0%) and neurological disease (10.3%) when compared with other co-morbidity; however, these numbers seemed compatible with associated co-morbidity for the general population of similar age (292) (293).
Examination of proportions of dysplastic disease and associated co-morbidities revealed no significant differences apart from – somewhat surprisingly - in patients with fibroid disease; where there appeared to be significantly higher proportions of HGD/AC. However, these numbers were very low with only 3 patients in the cohort having evidence of this condition, (2 of which developed severely dysplastic disease) and these results in isolation may need to be interpreted with caution.

There is very little documentation of specific associated co-morbidities that are thought to either play a role in the development of CLO or its progression to dysplasia and adenocarcinoma. Specific drug treatments for various conditions may have an impact on development and progression of oesophageal disease and are, perhaps, more relevant than the associated diseases themselves. NSAID therapy for example, in orthopaedic/rheumatological conditions is fairly common and its long-term use may have an impact on CLO. This particular study did not look specifically at medication and the resultant effects on reflux-induced oesophageal disease, which may be an area with some scope for further analyses.

Diagnosis of CLO

Grade of disease diagnosed

Although 90% of patients were diagnosed with non-dysplastic CLO at first 'diagnostic' endoscopy, 2.4% of patients were diagnosed with AC on first presentation. This represents a high number of patients presenting with late stage disease and a subsequent poor prognosis (the numbers that go on to develop what can be classified as prevalent AC – *see surveillance chapter* – makes this figure even more alarming).

31.6% of patients were originally diagnosed visually at endoscopy only (no initial histological confirmation of CLO), however 64.1% of these had confirmatory biopsies done at a later stage. In 4.7 percent of them, initial biopsies had been done but were negative for CLO. In the 2005 BSG guidelines (18) the definition of CLO states that disease must be confirmed or corroborated histologically. These guidelines also state that the absence of IM at index endoscopy does not preclude an accurate diagnosis, since British pathological opinion believes that if enough biopsies are taken over a long enough period of time, IM will inevitably be detected.

Interestingly, if US guidelines had been adhered to, where the presence of IM is a prerequisite for diagnosis, then this would have excluded 49.5% of the cohort from this study; 16.4 % of which went on to develop dysplastic disease (LGD or worse).

However, it was clear from the comparison of grades of disease diagnosed over time that there was more disease diagnosed with corroborative histology, *and* the presence of IM, in later time-bands (visual CLO: 11.2% of all disease in the latest time-band compared to 60% of disease in the earliest) (CLO + IM: 46.2% in the latest time-band vs 8% in the earliest).

There was also a trend towards a more frequent diagnosis of 'indefinite for dysplasia' and LGD over time. Whether this is a reflection of a real increase in prevalence of these grades of disease or whether histopathologists are tending to

look more for signs of early dysplastic change in the latter time-bands is impossible to say. There is evidence to suggest that interobserver agreement is the lowest for diagnosis of these grades of disease (161) as the distinction between this and benign regenerative/inflammatory changes may be difficult. 'Indefinite for dysplasia' as a classification of histological grade of disease would also have been sparsely used in the very early time-bands and this may account for its infrequent appearance in pathology reports around this time.
Frequency in the diagnosis of severely dysplastic disease – ie. HGD and AC - however, did not appear to vary significantly over time.

Length of the columnarised segment

58.1% of patients overall had a length of CLO documented on diagnostic endoscopy, with a significant higher frequency of documentation in the latter time-bands. Measurements for the length of CLO were not always documented on the endoscopy form but were able to be calculated from recordings of the level of the GOJ and SCJ in the vast majority of patients. Consistency in measurement of the columnarised segment has important implications both in estimating dysplastic risk on diagnostic endoscopy and in monitoring progression of disease in individuals with established CLO. In 2006, the 'Prague C and M' criteria was published in order to address this issue and to offer an explicit, validated criteria for endoscopic grading and diagnosis of CLO (174). The system – in which methods for recognition of anatomical landmarks and assessment of both circumferential (C) and non-confluent disease (maximum extent of disease = M) are outlined – was shown to have a high overall validity.

In our study, the mean length of CLO increased significantly with severity of disease diagnosed from non-dysplastic disease to HGD. This is in agreement with a number of studies (280) that suggest a higher risk of dysplastic transformation in longer segment lengths, and fits with the theory that links extent of acid exposure to length of columnarisation and subsequent disease severity. Interestingly, the mean length of diseased segment in patients with AC was less than those with

LGD and HGD; however, this may be explained by regression in length due to tumour retraction or fibrosis.

Proportions of short segment to long segment disease diagnosed did not vary much over time, with certainly no trend towards an increase in diagnosis of short segment disease over the last few years. This is not in agreement with some authors who have suggested that the vast increase in the prevalence of CLO observed recently has been largely due to an increase in short segment disease being diagnosed and argue that this may reflect a general 'over-diagnosis' of the disease (294).
In a study published by UKBOR in 2007 (280) which stratified segment length and risk of malignant transformation, however, the significant risk of short segment disease is highlighted, being equal to that of overall long segment disease (>3cm) but more than diseased segments between 3 and 6 cm. Whether the relatively high risk of short segment disease observed is due to the high levels of acid and nitrate exposure near the GOJ is debatable.

Non-confluent disease

7% of patients had evidence of non-confluent disease documented on endoscopy, with its presence much less frequent in more dysplastic disease. It may be that non-confluent or 'streaks' of columnarisation represent an earlier and less severe stage in the pathological process and that circumferential disease occurs as a result of more prolonged refluxate exposure and is therefore possibly a more important marker of oesophageal injury. Non-confluent disease was also diagnosed significantly less during the latter time-bands which may represent the fact that endoscopists are concentrating more on circumferential disease because of its perceived greater significance in terms of dysplastic potential.

In this study, we found that in patients with short segment disease (≤3cm columnarisation) and intermediate segment lengths (>3cm ≤6cm), higher proportions of circumferential disease were more likely to be associated with a

diagnosis of dysplasia than when non-confluent disease was present; however, in patients grouped into disease of lengths >6cm proportions of non-confluent:confluent disease did not seem to affect disease grade severity. It may be that once columnarisation has extended approximately 6cm or more then, irrespective of whether the disease is circumferential or not, this represents a certain level of refluxate exposure with an associated risk of dysplasia. Similarly short tongues of columnarisation probably represent a relatively low acid exposure.

Biopsy Protocol

The mean number of biopsies taken for the diagnosis of non-dysplastic CLO was 4.59 and increased as the grade of disease diagnosed worsened.
Whether this trend in increase in biopsy numbers arises as a result of the fact that dysplastic disease is more likely to be identified the more biopsies that are taken, or that endoscopists are inherently taking more biopsies if they suspect more severe disease based on the presence of macroscopic lesions (frequently associated with the more severe disease subtypes) is hard to say.

UK based evidence suggests that the likelihood of detecting IM increases with the number of biopsies taken, therefore, sampling error may prevent IM being detected at index endoscopy (295). This supports the argument that it is not unreasonable for a diagnosis of CLO to be made in the absence of histological confirmation of IM. In this analysis there was no significant difference between mean number of biopsies taken in the diagnosis of CLO where IM was found compared with CLO where no IM was evident, however, for the diagnosis of CLO –IM significantly less biopsies were taken when compared to *all other* disease types. The mean number of biopsies taken in the patients who had *no histological evidence* of CLO at diagnostic endoscopy (but who went on to have this diagnosed at a later stage) was no different from the mean number of biopsies taken for all other disease subtypes and it may well be the case that in a reasonable number of patients the presence of CLO or IM may just not be

demonstrable on that occasion. The introduction of more and better methods of targeted biopsying techniques - ie with stains or using magnification techniques - will hopefully improve the detection of these types of disease as well as the diagnosis of various grades of dysplasia.

There was a significant trend for greater numbers of patients with CLO and associated ulceration to be diagnosed in the more recent time-bands. There is a possibility that this has arisen as a result of endoscopists becoming more aware of disease associated with ulceration and the perceived inherently increased malignant risk or, perhaps more worrying, due to a real increase in more severe oesophageal disease.

Documentation of the practice of taking 4 quadrant biopsies was rare (6% of all patients), possibly because of the infrequency in this technique employed in the U.K. due to its associated increased histopathololgical workload and time-economic implications. However between 1994 and 1999 there was a significant increase in documentation of this practice (12.4% of all patients biopsied), which may possibly reflect reaction to the guidelines at the time, particularly in view of the publication of Levine's paper in 1993 stating that taking biopsies using this technique significantly improved diagnostic distinction between HGD and AC. Of the patients biopsied with a 4 quadrant technique, 28.6% (16/56) were diagnosed with dysplastic disease (LGD or worse). This is compared to 10.2% (112/1098) of patients diagnosed with dysplastic disease having had biopsies taken without incorporating this technique ($p<0.001$, chi-square). It is possible that endoscopists are biopsying with this technique when there is suspicion of dysplastic disease based on an abnormal macroscopic appearance (a raised lesion or ulcer for example), however, it may be that the technique is more sensitive in picking up dysplastic disease. Interestingly, there does not seem to be any significant difference in proportions of *severely* dysplastic disease (HGD or worse) diagnosed when incorporating this technique.

Comparison between centres

Proportions of disease diagnosed

Frequency of HGD/AC diagnosed between the centres varied from 0.8-6.7% of all disease diagnosed, however, there were no statistically significant differences between the centres when compared as a proportion of all diagnoses.

The proportion of CLO diagnosed with IM varied significantly between the centres compared to CLO diagnosed without IM, as did frequency in diagnosis of CLO without any histological corroboration. This is likely to be a reflection of endoscopist and histopathologist individual practice rather than a representation of varying grades of disease amongst the populations. Varying work demands on histology departments particularly may affect rates of histologically confirmed CLO, with endoscopists more likely to make a purely visual diagnosis if they work in conjunction with over-stretched histopathological departments.

Frequency of indefinite for dysplasia and LGD also varied significantly between the centres and may reflect the documented inconsistency in interobserver agreement in the diagnosis of these grades of disease (161).

Length of CLO

The proportion of patients with documentation of length of columnarisation on diagnostic endoscopy varied from 26.0% (centre 2) to 86.6% (centre 3). On analysis, there were higher proportions of long segment disease diagnosed in centre 1 and higher proportions of short segment disease in centre 5. Whether this represents a real difference in disease severity between these two populations (both centres were in the north of England), or whether it represents inherent endoscopist bias in the diagnosis of these types of disease is difficult to say. The recognition of short segment disease (particularly more than 10 years ago) varies between endoscopists, as the malignant potential of this pathology is by no means widely accepted.

The documentation of non-confluent disease was significantly more frequent in centre 5 and, again, may have reflected the interests and practices of this

particular endoscopy unit. From our results it appears that circumferential disease is much more commonly associated with dysplastic disease and it may be that the other centres are tending to concentrate on this morphology of disease for this reason.

Biopsy Protocol

There were some variations between the centres in mean number of biopsies taken when diagnosing varying grades of disease, however, in terms of real numbers these only varied by 1 or 2 biopsies for the majority of analyses.

Centre 5 was the only centre that took reasonable numbers of biopsies with documentation that a '4 quadrant biopsy technique' was employed (14.5% of all diagnostic endoscopies), and again is likely to reflect the policy of that particular endoscopy unit. However, it is interesting to note that although centre 5 was taking significantly more biopsies than the other centres it was still only taking a mean of 5.3 biopsies per diagnosis.

Helicobacter Pylori

Reports of the prevalence of *H pylori* infection in oesophageal disease vary from 14-40% in GORD/oesophagitis and 25-62% in CLO (191) (213) (296) (297) (209) although the prevalence of *H pylori* in oesophageal adenocarcinoma seems to be much less and reports have suggested anything from 0-20% (212) (213) (191). From our study the prevalence of *H pylori* infection in the patients that had been tested was fairly high at 55.7%. Even if the rest of cohort are taken into consideration, and it is assumed – although unlikely - that potentially they could all be *H pylori* negative, this would still give us a prevalence of 24.5%. As this is more than likely to be higher, then it may well be that prevalence of *H pylori* in the entire cohort would be greater than the reported prevalence of infection in normal/control populations which ranges from 17-36%; however, whether it would reach reported prevalence rates seen in patients with PUD (48-94%) seems unlikely (296) (212).

Demographics and patient characteristics were similar between the two groups. Follow up in the *H pylori* negative group, however, was significantly shorter and whether more dysplastic disease would have developed over a longer period of time is debatable.

Overall, patterns of disease distribution and endoscopic findings relating to oesophageal disease severity were remarkably similar between the two groups with no significant differences between any of the parameters examined. This seems to support the theory that *H pylori* may play little or no role in the progression of reflux-induced oesophageal disease. However, whether the predicted high prevalence of *H pylori* in the entire cohort could suggests a role in the initial pathogenesis of the disease is a possibility.

Recent studies have continued to fail to demonstrate consistent relationships between GORD, CLO and *H pylori* infection, however, it seems increasingly evident that other patient factors, such as age, ethnicity and patterns and strain of *H pylori* infection, may play a role in aetiology of the disease.

A study by Rajendra et al has shown that in high *H pylori* prevalent Asian populations, particularly Indians, infection may protect against oesophageal reflux disease, whereas this effect is not so obvious in ethnic groups such as Malays where prevalence is much lower (298).

In an epidemiological study on a Swedish population the presence of *H pylori* infection in conjunction with reflux symptoms was found to have a 5-fold risk on development of CLO (299) and similarly a Spanish study done by Ferrandez et al on a population with a high prevalence of *H pylori* (74.6% infection rate) demonstrated a higher prevalence of infection in patients with CLO compared to controls (300).

Patient genetic factors have been suggested to have an effect on host response to infection. It has been proposed that a polymorphism of the interleukin 1B (IL-1B) gene cluster may lead to an augmented IL-1B secretory response to *H pylori* infection, resulting in an abnormally increased suppression of acid production and predisposition of gastric atrophy and gastric malignancy in the long-term (301). The long-term effects of this on oesophageal tissue, however, is less certain, but links with decreased E-cadherin expression and increased catenin regulated transcription factors – both found to be associated with neoplastic progression of CLO – have been observed (302).

An unexpected finding from this study was that the frequency of associated gastritis and duodenitis did not seem to be any higher in the *H pylori* positive group. This may be a reflection of the fact that the vast majority of these patients would have been on long-term acid suppression treatment and therefore clinical evidence of gastro-duodenal disease limited. There is also some evidence that *H pylori* positive patients on proton-pump inhibitors or H2 receptor antagonists show a greater level of acid suppression (303) (304); an observation that has added weight to the argument that infection need not be eradicated in patients with oesophageal disease.

On the other hand long term proton pump inhibitor therapy has also been shown consistently to alter the distribution of *H pylori* from an antral to a corpus or

fundus predominant pattern; an alteration that enhances the progress of atrophic gastritis and thus the risk of gastric cancer (305).

Whether or not to treat *H pylori* infection in these patients, therefore, is still controversial and consensus remains to be achieved.

Interestingly, in our study 571/1000 (57.1%) patients with CLO were *not* tested for *H pylori* at any time over their follow-up, and of those that were only 27.6% of patients who were positive underwent eradication therapy.

Surveillance

Surveillance programmes

From this study, we observed a greater than 69% documented surveillance programme enrolment in all but two of the centres. In patients that had had a relatively recent diagnostic OGD only, it was impossible to predict whether or not they would have gone on to have had further surveillance endoscopies or not, so that the actual proportions being surveyed is likely to be much higher than stated (when the 'diagnostic OGD only'group are excluded, the proportion undergoing surveillance is > 96.5 % in all centres). A high frequency of surveillance in these patients is not unexpected due to an inherent bias in the UKBOR cohort, in so much that Registry patients – by nature of their 'selection' onto the database – are likely to have been followed up by gastroenterologists with an interest in CLO (or at least in a centre where the 'lead' gastroenterologist has such an interest). Interestingly, this high proportion of surveyed patients included some who were initiated onto surveillance programmes almost 25 years ago; 12 years before the first formal guidelines for surveillance were published. The few patients not enlisted onto programmes were deselected due to specific medical or social regions, usually because of their age.

Patient demographics

The mean age at diagnosis in the surveillance cohort was 61.2 years, which is similar to findings from previous studies (131, 133). The 'non-surveillance cohort' (ie those specifically selected out of surveillance) were significantly older (being diagnosed approximately a decade later), as expected.

There were some differences in age at diagnosis between the centres with centre 4 being significantly younger and centre 6 significantly older. This may be explained by geographical/cultural differences between the centres. Centre 4 is the only centre examined from Scotland, and studies have shown a high prevalence of CLO in young people from this region in particular (288). Centre 6 is located just

south west of London and may represent characteristics of a slightly older – and possibly more affluent – population in general.

The gender distribution – with a higher proportion of males to females in all centres– was expected based on Registry data on the characteristics of patients with CLO (133).

Differences in disease distribution at diagnosis seemed to mainly reflect proportions of LGD diagnosed, with the highest proportions observed in centre 1. This may represent varying criteria in the diagnosis of LGD between the centres rather than a true reflection of numbers of patients with dysplastic disease. Consistency in diagnosis of LGD has been documented as being fairly low, and may well explain this observation (160).

A similar finding was in the diagnosis of 'indefinite for dysplasia', where the presence of regenerative/inflammatory changes can make a definitive diagnosis of dysplasia very difficult.

Surveillance interval

From this study, we observed that the more severe the grade of histology, the shorter the subsequent endoscopic surveillance interval, as predicted. However, for surveillance of non-dysplastic CLO the actual mean time interval – 1.29 years - seems shorter than would be expected, especially as most guidelines do not recommend surveying more frequently than biennially.* Surveillance seemed particularly frequent for disease classifications 1 and 2 (visual Barrett's only; and CLO on histology – no IM). A possible reason for this is that an immediate follow-up endoscopy post-diagnosis may be done fairly quickly in order to 'confirm' the original diagnosis. Other studies looking at surveillance intervals have excluded this 'first interval' in order to give a more realistic impression of timings between endoscopies. Another explanation, however, may be that these endoscopists are surveying more frequently as a reflection of their inherent bias in interest in the management of CLO.

* Interestingly, however, the survey done by Smith et al found that 55% surveyed at yearly intervals (257)

As a comparison between the centres, surveillance intervals for non-dysplastic disease and HGD were similar in all centers, however, surveillance intervals for LGD varied considerably. This may reflect the fact that evidence in the literature for frequency of surveillance for LGD is controversial – ranging from 3 monthly to yearly – and also variation in inter-observer consistency in making the diagnosis in the first instance.

In a mathematical model published by Provenzale in 1994 (256) precise surveillance intervals were calculated in relation to life expectancy and morbidity in patients with CLO. Interestingly they found that initially the optimal endoscopic interval for maximal life expectancy was yearly; and when this was adjusted for quality of life (incorporating the morbidity of endoscopy and oesophagectomy), then the interval increased to 2-3 yearly. Very few studies have examined surveillance interval and impact on survival in clinical situations. Recommendations for surveillance intervals for non-dysplastic CLO from published studies range from 1 to 5 years (168) (264) (262).

Mathematical models based on UK AC incidence data have suggested intervals of 2 yearly for patients with non-dysplastic CLO (306) and hence the current UK guidelines recommend this interval.

Detection of dysplasia

There were no significant differences in detection of worsening histological grade per surveillance interval except for patients being surveyed with a diagnosis of LGD. In these patients shorter intervals – 0-3 monthly - corresponded to a significantly higher detection rate of HGD and AC. We found that the patients being surveyed at these shorter intervals were statistically more likely to have had a higher proportion of macroscopic lesions at diagnosis – namely ulcers or strictures – which may explain the shorter interval and the fact that they are inherently more likely to progress to more severe disease.

Interestingly, the most recent guidelines from the USA (264) recommend *annual* endoscopy for LGD, despite previous authors suggesting repeat OGD and biopsy after 3 months for patients with low and moderate grade dysplasia (260) and

studies that have shown that most people (90%) survey LGD at intervals of < 6 months (30% 3 months or less) (261). Current BSG guidelines recommend 6 monthly endoscopies for persisting dysplasia (18).

The evidence for risk of progression of LGD to HGD/AC, and the time that this might take, is controversial. Some series have shown very little evidence of malignant transformation even after 7 years or more of follow-up (307) (308). Some studies, however, have shown progression to adenocarcinoma from LGD within 4-5 years (308) (309).

It appears that there are some differences in either frequency of 'detection' of dysplasia (LGD or worse) or in actual 'progression' to dysplasia between the centres. Although there are various patient characteristic differences between the centres that could possibly affect progression to dysplasia rates (centre 2, for example, has a high rate of detection/progression to dysplasia and a high male:female ratio), this seems fairly unlikely, particularly as one of the centers with the lowest progression to dysplasia rates (centre 6) also had a significantly older cohort. A more likely explanation, therefore, may simply be due to varying criteria for histopathological diagnosis of dysplasia between the centres, with some showing a trend towards diagnosing this more readily than others.

Oesophageal adenocarcinoma

On examination of the cancers diagnosed in the surveillance cohort 37.1% were prevalent and 62.9% true incident cancers (diagnosed > 1 year from initial CLO diagnosis). 71.4% of all the cancers detected on follow-up endoscopy were done so at specific endoscopies documented for surveillance purposes, with 59.1% of patients having had true incident cancers detected at specific surveillance endoscopy.

When survival times in those surveillance detected cancer patients were compared to those detected on endoscopy for new symptoms, there was a trend towards an increased survival in the surveillance detected group; although this did not reach statistical significance on cox regression analysis.

On further analysis of surveillance detected cancers compared with *all* other cancers detected on non-surveillance endoscopies (ie including the 'non-surveillance' cohort), there remained a trend towards increased survival in the surveillance group – which was almost *double* that of the non-surveillance group (2.0 vs 1.1 years) - however, this did not quite reach statistical significance on cox regression analysis (p=0.072). It was postulated that these findings may simply be reflecting a lead-time bias and that the only clinically relevant data would be to measure impact on survival rates after some sort of intervention. Therefore, patients undergoing surgery (oesophagectomy) for AC were examined and a comparison made between survival in those who had been diagnosed on surveillance endoscopies and those that hadn't. The results demonstrated an increased survival in the surveillance detected cancers (2.43 years) compared to the other cancers (1.84 years) with a 30% reduction in hazard ratio for those under surveillance, but the analysis was done on a fairly small cohort of patients and again, these results failed reach statistical significance.

Several reports from the literature have suggested a survival advantage in patients undergoing surgery having had their cancers detected whilst on surveillance compared to those detected on endoscopy performed for symptomatic reasons (253) (128) (255) with a greater than 80% survival rate at 2 and 5 years in surveyed patients. Criticism of these and other studies, however, has been that they are almost all carried out retrospectively and on relatively low numbers of patients.

Provenzale (256) calculated that in order to set up a randomised controlled trial to detect a 50% reduction in cancer mortality rate - assuming an annual incidence of AC of 1.3% in patients with CLO - it would be necessary to enroll 5000 patients with a 10 year follow-up period. It is therefore, perhaps, not surprising that in conjunction with the ethical dilemmas that a prospective randomised controlled trial ensues, a study of this sort is yet to exist.

High-grade dysplasia

From our cohort 32.4% of patients with HGD were referred directly for surgery, with 3 of the centres making these referrals. In the literature, proportions of patients with HGD referred directly for surgery varies from approximately 23% to 73% (257) (258) (261).

50% of patients in our study underwent what could be defined as a period of true endoscopic surveillance (mean interval 8.6 months) with all of the centres surveying a proportion of patients. 41.2% of all patients with HGD progressed to adenocarcinoma at some point in their follow-up. Early surgery for HGD did not seem to offer any survival benefit over surveillance and surgery for AC once developed, and, in fact, there was a trend towards longer survival in the surveillance group. However, the direct mortality rate from surgery itself was not incorporated into this analysis, and it is recognized that this is likely to have affected these results. Whether this should strengthen or weaken the argument for close surveillance rather than surgery for HGD, as advocated by some authors (74), is a contentious issue.

The natural history of HGD is unclear. Although some studies have suggested an average time for progression to AC in the region of 24 months (165) (308) (77) (164) not all patients with HGD appear to progress to HGD and regression of HGD to LGD or no dysplasia is well documented (164) (190) (310). Although surgery for HGD will prevent progression to AC there have been no studies demonstrating that this offers a clear benefit in overall survival compared with close surveillance and surgery if and when AC is detected. The advent of new less invasive techniques, for example LASER, PDT and endoscopic mucosal resection, will undoubtedly affect management of HGD in the future.

Biopsy technique

The worse the disease being surveyed, the more the number of biopsies taken on surveillance as would be expected. It is likely that physicians are more concerned of the possibility of malignant disease if the histological grade has already progressed and therefore tend to 'look harder' for underlying malignancy.

Documentation of a '4 quadrant biopsy technique' was extremely infrequent from examination of the endoscopy/histology reports. This may well reflect a reluctance to use this technique in the U.K., perhaps due to limitations on pathologist's time and lack of resources to support such an intense biopsy protocol.

Factors affecting surveillance interval

Patients endoscoped at shorter intervals were significantly more likely to have been diagnosed with strictures or ulcers at diagnostic OGD ($p=0.002$) ($p=0.046$). This is not surprising as the presence of both oesophageal strictures and ulcers are known to be a significant risk factor for the development of dysplastic disease and patients with these conditions are also more likely to require close surveillance for ongoing symptomatic review. Independently, however, the presence of macroscopic lesions did not seem to have a significant effect on surveillance interval; with only age and grade of disease showing statistical significance on multiple linear regression analysis.

Other associated upper GI disease including duodenitis, DU, gastritis, GU and oesophageal polyps, also failed to demonstrate a significant association with endoscopic interval employed.

Endoscopist survey

A 70% response rate by the lead endoscopists was felt to represent a fairly good proportion of UKBOR registering centres; however, it is debatable as to whether this gives an accurate indication of practice in the U.K. as a whole. The lead endoscopists of these centres, by virtue of the fact they have registered patients with UKBOR, are likely to have an interest in the management of CLO and it is likely that the rest of the U.K. may not be as proactive in their management. (Overall, 44% of all endoscopists contacted replied to the survey and, again, it is recognised that there is a likely bias towards a more proactive approach to the management of CLO amongst this group as a whole.)

Several guidelines for the diagnosis and management of CLO and its complications have been published over the last 10 years (264) (166) (18). Recent UK guidelines (18) have highlighted a number of areas including definition of the columnar segment, the need for corroborative histological evidence for an accurate diagnosis, and recommendations for surveillance programmes for non-dysplastic and dysplastic disease.

Less than half of the centres examined admitted to having a formal, written policy for the management of CLO that was distributed throughout the department and available to both junior and senior endoscopists. Of those that did, 6 centres sent a copy of these guidelines with the completed questionnaire as requested. These guidelines were all designed by and individual to that specific department and easily accessible to the endoscopists (one in the form of an online document). The vast majority only gave guidance on surveillance – rather than diagnosis – but included strict policies on which patients should be surveyed, what the appropriate endoscopic interval should be, specific biopsy protocol and recommendations for further follow up and management based on the grade of disease diagnosed.

Some centres at the time of the questionnaire said they were awaiting the publication of more formal guidelines before committing the department to a formal protocol.

It seems that most endoscopists were recognising the importance of short segment disease with only a minority requiring a length greater than 3 cm in order to make a diagnosis. Also, isolated mucosal islands and streaks or non-confluent disease alone were being treated as Barrett's by the vast majority. This trend to veer away from the historical classification of circumferential CLO of greater than 3 cm is backed by evidence suggesting that both short segment and non-circumferential disease have significant malignant potential (311) (280) and is reflected in the current BSG guidelines that suggest that any portion of the normal squamous lining thought to have been replaced by columnar epithelium on endoscopic examination should be regarded as pathological.

Endoscopists were fairly consistent in documenting their findings and in giving measurements for the length of disease and precise anatomical landmarks, however, information documented on histology request forms sent to the pathologists were not so detailed – with only 62% of all endoscopists documenting the level of the biopsy site and 33% recording the level of the GOJ. Guidelines recommend that all disease should be biopsied and a diagnosis of CLO corroborated histologically. However, although the majority of endoscopists biopsied all patients at first diagnostic endoscopy, 27% didn't, and, in fact, 33% of all endoscopists said they would survey non-histologically proven disease anyway.

44% said that they would survey disease with evidence of columnar or gastric-type epithelium on biopsy but no evidence of IM, and this possibly reflects the current views in the U.K. that a diagnosis of CLO does not necessarily require the presence of IM on histological examination.

The vast majority of endoscopists (80%) practiced a selective surveillance policy; although, in those centres that did survey, overall endoscopic intervals were fairly consistent, particularly for non-dysplastic disease. Surveillance intervals for indefinite and low-grade dysplasia were slightly less consistent, however, and may have well have either been a reflection in varying diagnostic criteria between the centres for these grades of disease- with difficulty in distinguishing between regenerative/inflammatory cellular changes and true dysplasia – or in the lack of

evidence in the literature for recommendations of precise endoscopic intervals for these types of changes.

Overall, however, reported surveillance intervals seem to correlate fairly well with the published guidelines which recommend an interval of 2-3 yearly for non-dysplastic CLO and 6 monthly for LGD.

For HGD, the current BSG guidelines recommend immediate re-biopsy and confirmation by two expert pathologists with a view to surgical referral if HGD persists and this correlates with similar guidelines published in the USA within the last 3-4 years. From this study, however, although 89% of all endoscopists adopted a policy of frequent surveillance (87% between 1 and 6 monthly) it was unclear as to whether these centres would survey over a long period of time or if they would make a referral to surgery for persisting disease. Only 5 endoscopists said they would make a direct referral for surgery in the first instance.

The majority of endoscopists stated that they used a '4 quadrant biopsy technique at 2cm intervals' for both diagnostic and surveillance endoscopies, although very few said that they used jumbo-sized forceps routinely. The widespread use of a 4 quadrant biopsy technique, as originally described by Levine in 1993 (165), has been heavily debated over recent years with much criticism with regards to the increased work intensity – particularly on the pathology department – that it ensues, and it is perhaps surprising that such a large percentage of centres said they regularly adopted this technique.

Very few endoscopists felt that 'stable' or regressed disease over a period of time was a reasonable indication for cessation of surveillance, however, the majority agreed that age, significant co-morbidity or unsuitability for oesophagectomy may influence their decision to stop endoscopic follow up.

The relationship between *H Pylori* and CLO is controversial and has been discussed earlier. From this study it was observed that less than 50% of physicians said that they checked for *H pylori* routinely at diagnostic endoscopy, with most reserving testing only for patients with associated gastro-duodenal inflammation or ulceration.

In summary, the practice of diagnosis and surveillance of CLO varies throughout the U.K. Although diagnostic criteria for CLO appears to be fairly consistent for recognition of the disease at endoscopy, a requirement for corroborative histology is by no means universal, and a number of centres are still diagnosing and following up non-histologically proven disease. A large number of centres now survey CLO – undoubtedly more than were surveying 10 years or more ago – with most centres continuing to adopt a selective surveillance policy; however, amongst those who do survey, endoscopic intervals and biopsy techniques seem to be reasonably consistent.

This survey was conducted prior to publication of the 2005 BSG guidelines (18) and it will be interesting to monitor the effect of these on consistency of diagnostic and surveillance practice in the future.

Summary of findings/Contribution to science/Future research

Summary of main findings:

This is a large cohort study of patients with established columnar-lined oesophagus examining patient risk factors for the development of dysplastic disease, diagnosis of all grades of disease and the use and impact of surveillance techniques in managing these patients.

1. Male gender, smoking and age were the only patient characteristics consistently found to be significant risk factors for development of dysplastic disease.
2. Greater lengths of columnarisation and higher proportions of circumferential disease were found to be significantly associated with findings of dysplasia.
3. The presence of Helicobacter pylori infection was not found to be a risk factor for development of worsening oesophageal disease.
4. Shorter endoscopic intervals for surveillance of LGD were significantly associated with more frequent detection of severe dysplasia.
5. Survival in patients who had their AC diagnosed whilst on surveillance was significantly greater than patients who had their AC diagnosed for other reasons.
6. Surgery for HGD did not offer any significant survival advantage over continued surveillance.

Endoscopic survey findings:

1. There were inconsistencies in the management of CLO between endoscopists and endoscopy units throughout the U.K.
2. Practice has changed over the last 10 years with an increase in diagnosis of short segment and non-confluent disease and a tendency for increased surveillance of CLO in general.

Many of these findings add weight to the evidence for the basis behind recent publication of formal guidelines on the diagnosis and management of CLO; ie, diagnosis and surveillance should be targeted towards high risk groups – males, age >55 years, smokers, specific disease morphology such as longer segments and circumferential disease (although recognition of the malignant potential of short-segment disease should be recognised.) Our findings emphasise the risk of development of dysplastic disease in smokers and specifically brings attention to the high risk in ex-smokers. We have demonstrated a lack of relationship between *H Pylori* and development of worsening disease in patients with established CLO, but have not ruled out the possibility that *H pylori* may play a role in the initial aetiology of columnarisation, and note the presumed high prevalence of infection in the cohort as a whole. It may therefore be of benefit to test and treat patients with simple oesophagitis- prior to the development of columnarisation; however, routinely testing all patients with established CLO is probably less important from an oesophageal point of view.

Our findings examining survival in patients with AC support the evidence that surveillance helps to detect cancer at an early stage and that patients undergoing surgery for surveillance detected disease have a trend towards increased survival. Surgery for HGD, however, does not seem to offer any survival advantage over surveillance alone; and therefore close endoscopic and histological follow-up with surgery for AC if develops should be considered.

Recent findings/new developments

Diagnostic techniques

The use of chromoscopy and endoscopic fluorescence for the detection of CLO and dysplasia have already been mentioned and have not been recommended for routine use in the most recent BSG guidelines. Newer techniques such as ELASTIC scattering spectroscopy and endosonography are in the developmental phase but may prove useful diagnostic tools for the future. Optical coherence tomography and optical biopsy (312) (313) are fairly new techniques that are currently still under evaluation for potential use in the future.

Molecular biology/Oncogenes/genetic therapy

Molecular markers of epithelial dysplasia and risks of impending cancer have been studied for other diseases and their role in AC examined. These include p53 mutations, p16 mutations, cyclin D1 over expression, decreased E-cadherin expression and loss of heterogenecity of adenomatous polyposis coli genes (314) (315).

'Diffuse gastro-oesophageal cancer syndrome' has been described (316), but familial gastro-oesophageal cancer syndromes are rare, and may account for 1-5% of cases.

Levels of E-cadherin – a protein involved in cell adhesion and found to be important in tumour suppression (317) – have been shown to be reduced in oesophageal tissue during progression from CLO to AC, and a germline mutation of the gene coding for this has been demonstrated in patients with familial diffuse gastric cancer syndromes.

E-cadherin associates with a cytosolic protein called B-catenin in order to form an adhesion complex. Non-complexed B-catenin, once degraded, has been shown to bind to a specific nuclear transcription factor (of the LEF-TCF family), which promotes oncogenic target genes, which induce proliferation such as COX-2, c-myc and Cyclin D1 (317). Increased nuclear localisation has been observed in oesophageal tissue progressing through stages of dysplasia.

In the recent BSG guidelines, a number of molecular and genetic markers relevant to CLO and its progression to cancer, including the ones discussed above, are mentioned, although their uses at present are largely recommended for the confines of research.

Anti-cancer drugs

The role of anti-inflammatories on cellular proliferation and angiogenesis is controversial, but there is some evidence to suggest they may act in preventing dysplastic change in CLO, particularly as chronic inflammation of the oesophagus has been implicated in AC development (97).

The U.K. *AsPECT* (Aspirin, Esomeprazole, Chemoprevention Trial) trial has been set up largely to examine this, and at present is in the process of recruiting between 5000 and 9000 patients with CLO.

Advances in LASER/photodynamic therapy

LASERs such as Nd-YAG and GaAIAs, and the less expensive Argon plasma coagulators, are all currently in use for ablation of metaplastic and dysplastic oesophageal mucosa. Photodynamic therapy (PDT) has been shown to be a relatively safe technique for the treatment of metaplasia and dysplasia although there is a 30% associated risk of stricture formation where mTHPC or Photofrin are used as photosensitisers (318). The development of newer light delivery systems and photosensitisers may reduce these complications and improve overall efficacy. Current BSG guidelines, however, suggest that these techniques be limited at present to prospective randomised studies and reserve recommendation for their routine use until more evidence has been collated.

Future studies

Patient characteristics

Large cohort studies will continue to help in highlighting patients at risk of the development of CLO and dysplastic disease. The ongoing collection of data by registries such as UKBOR, with active recruitment of registering centres and detailed recording of patient information, should allow construction of large informative databases from which meaningful information can be extrapolated. In order for risk factors for the development of CLO per se to be assessed, control groups – either patients with reflux but no CLO, or 'normal populations' - need to be included as part of this data gathering.

More detailed studies on obesity and risk of development of CLO and progression to AC are recommended, particularly in view of current trends in body mass indices observed in Western societies over the last few years.

Epidemiological studies incorporating data on ethnicity, cultural diversity, social class and dietary habits could all yield valuable information with regards to risk factors for CLO and its progression, and could help to identify patients at risk of progression to AC.

Diagnosis of CLO

Further cohort studies over longer periods of time will add weight to previously published data on the stratification of length of CLO diagnosed, proportions of non-confluent disease observed and subsequent risk of dysplasia.

A large prospective randomised controlled trial, with adequate follow-up, looking at varying diagnostic biopsy regimes for various grades of disease could help establish an acceptable and sensitive biopsy protocol.

H pylori

In order to clearly assess the effects of *H pylori* infection on development of CLO and progression of reflux-induced oesophageal disease, studies should be designed to examine precise distribution and patterns of *H Pylori* infection on

endoscopy and histological examination, and include an accurate record of pharmacological intervention over a substantial follow-up period. There is potential for a prospective randomised trial of eradication versus no eradication in patients with established CLO, and/or in patients with less severe reflux disease.

Surveillance

There have been a number of studies examining whether surveillance endoscopy detects AC at an earlier stage of disease and the impact this has on subsequent survival. Few studies, however, have looked at detection of pre-invasive disease on surveillance and analysed whether this has an impact on survival – or development of AC - in this group of patients. From our study, approximately 95% of patients diagnosed with LGD or HGD were picked up on specific surveillance endoscopies. Intervention at these early stages in the disease – especially with the advent of new types of LASER and photodynamic therapy - may prove to have a significant impact on progression of disease and long-term survival. A study comparing long-term outcome in surveyed versus non-surveyed patients with this type of disease would be very interesting.

The question of how frequently to survey patients with particular grades of disease is hard to answer. This study showed an increased detection of severe dysplasia/invasive cancer when LGD was surveyed at shorter intervals but the significance of this with regards to patient outcome was not examined. A study looking at the impact on patient management and overall survival between patients diagnosed early with dysplastic disease compared to those diagnosed later (those surveyed at 3 monthly intervals vs those surveyed yearly, for example) could yield some valuable results.

The true effectiveness of surveillance programmes in patients with CLO is hard to assess without the benefit of a prospective randomised trial. Ethical considerations, however, may make this form of study hard to construct and hence, to date, no trials have been carried out.

Appendix

.....

Appendix 1: Form 1

UK National Barrett's Oesophagus Registry

A Joint BSG / ECP Initiative

Reg. Form 1 Date: ___ / ___ / ____

Patients Name: _____ Address: _____

Sex: (M/F/NK) _____ _____

Date of Birth: ___ / ___ / ____ _____

NHS Number: _____ _____

_____

Hospital: _____ Hospital Address: _____

Consultant _____ _____

Patient's Hospital No _____ _____

Date of Diagnosis: ___ / ___ / ____ _____

Age at Diagnosis: _____ Contact Name: _____

Basis of Diagnosis: Contact ☎ No _____

Biopsy 1st endoscopy (Y / N / NK) Contact fax No _____

Biopsy at later endoscopy (Y / N / NK)

Visual diagnosis (Y / N / NK)

FOR OFFICE USE ONLY

Registry No:						

NK: Not Known

Appendix 2: Form 2

Date of form completion_____

Data Collection Sheet Dysplasia yes ☐ no ☐ AC yes ☐ no ☐

Name	
Hosp no.	
NHS no.	
DOB	
Address	
GP	

Sex Male ☐ Female ☐

Civil State Single ☐ Married ☐
Not known ☐ Divorced ☐
Widow(er)ed ☐

Ethnicity

Arabic	☐	Bangladeshi	☐
Caucasian	☐	Chinese	☐
Indian	☐	Pakistani	☐
Asian other	☐	Black African	☐
Black Carib	☐	Black other	☐
Other	☐_____		

Date of death	
1a	
1b	
1c	
2	

Main Occupation	
Retired etc.?	

Weight (Kg)

Date	Wt	Date	Wt	Date	Wt
				Height	**m**

Smoking (tobacco type/day)

Date	Amount	Date	Amount	Date	Amount

Alcohol (type, units per week)

Date	Amount	Date	Amount	Date	Amount

Symptoms

History length			
Retrosternal pain	**UGI Bleed**	**Nausea**	
Epigastric pain	**Odynophagia**	**Vomiting**	
Acid regurg	**Weight loss**		
Dysphagia	**Belching**		
Lifestyle Modification			

Medical History

Surgical History

Oesoph Dilation		**Date**	
Fundoplication		**Date**	
Cholecystectomy		**Date**	
Gastric Outlet		**Date**	

Medication History

Drug Date								

Family History

Blood Group	

Endoscopy/Other Imaging

Date	OGD/ Ba etc.	Oesoph	Stomach	Duo	Histol	HP test	HP Rx

Comments

Appendix 3: Database Tables

General table

UKBOR no.	Social class	***Co-morbidity:***	Cardiovascular notes
Form 2 done	Working	Neurological	IHD
Consent	Height	Gastrointestinal	CCF
no further info	Blood group	Achalasia	PVD
suspect diag	Last info	Mediastinal dxt	Arrythmias
data entered	Date surveillance stopped	IBD	CVA/TIA
surname	Reason surveillance stopped	Appendicectomy	HT
forename	Family history	Bowel op	DM
sex	Pt address	CA stomach	Endocrinology notes
Date of birth	GP address	Ortho/rheum	CA prostate
Date diagnosis	***Symptoms:***	CA colorectal	Lumps/Bumps
Hospital no.	Date symptoms	Liver disease	Thyroid disease
Date form 2	Heartburn	Gastrointestinal notes	Lumps notes
NHS no.	Epigastric pain	Genitourinary	Pneumoconiosis
Marital status	Abdominal pain	BPH	CA lung
Ethnicity	Acid regurgitation	Prostatectomy	**UGI procedures:**
Death certificate	Nausea	Fibroids	Oesophageal dilatation
Date death	Dysphagia	Hysterectomy	Cholecystectomy
Cause death 1a	Vomiting	Haematological	Cholecystectomy notes
Cause death 1b	Belching	CA breast	Fundoplication
ICD code 1b	Odynophagia	CA skin	Fundoplication notes
Cause death 1c	Anaemia	Respiratory	Gastric outlet surgery
Cause death 2	UGI bleed	COPD	Gatric outlet sx notes
D cert AC no.	Weight loss	Respiratory notes	AC treatment
Occupation	Night symptoms	Cardiovascular	AC treatment notes

Endoscopy table

UKBOR number	Hiatus position (cm)	AC present visually
Date OGD	Oesophagitis grade	Notes (AC)
Indication	Streaks of oesophagitis	Gastritis
SCJ position (cm)	Oesophageal ulcer	Gastric ulcer
Non-confluent disease	Hiatus hernia	Duodenitis
GOJ position (cm)	Oesophageal stricture	Duodenal ulcer
Visual diagnosis CLO	Oeso stricture site (cm)	
Stated length CLO	Dilatations done	

Histology table

UKBOR no.	Intestinal Metaplasia	Indefinite dysplasia (inflamed)
Date histology	Intestinal Metaplasia (incomplete)	Indefinite dysplasia (non-inflamed)
Histology site (cm)	Gastric mucosa	Low grade dysplasia
No. of biopsies	Gastric body mucosa	High grade dysplasia
4 quadrant biopsies	Gastric carditis	Adenocarcinoma
Squamous mucosa	Disorderly cardiac glandular mucosa	Helicobacter pylori present
Oesophageal glands	Acute inflammation	Other
Columnar mucosa	Chronic inflammation	

Drug table

Table 1	Table 2
UKBOR no.	UKBOR no.
Date	Drug ID
PPI	Dose
H2 antagonist	Start date
Aspirin	Stop date
NSAIDs	
Steroids	
Beta blockers	
Ca antagonists	
HP treatment	
Others	

Smoking table

UKBOR no.
Date
Score

H Pylori table

UKBOR no.
Date
Test type
Positive

Alcohol table

UKBOR no.
Date
Score

Weight table

UKBOR no.
Date
Weight

Appendix 4: Endoscopist questionnaire

UK National Barrett's Oesophagus Registry

Royal Free Hospital

London

Endoscopist Questionnaire 2004

Please write the name of the hospital you are currently working in

……
……

Does your department have a formal policy/set of guidelines on criteria for diagnosis of Barrett's Oesophagus and subsequent management?

If **Yes**, please answer **part A)** and enclose a copy with the questionnaire

If **No**, please answer **parts B)** and **C)**

Part A)

Please circle appropriate answer, or write in the space provided:

i) Is this policy/guidelines displayed in the department or easily accessible?

YES NO

ii) Is it made available to new doctors on joining the department?

YES NO

iii) Are the doctors expected to strictly adhere to the policy or are they just 'guidelines'?

.....

iv) Has this policy replaced a previous one? *(if so, please send both)*

YES NO

Please add any further comments :

.....
.....
.....
.....
.....
.....

Part B) Diagnostic Criteria

Please circle appropriate answers or write in space provided

1. On initial endoscopy would a diagnosis of BO be made if :

a) *Any* length of 'Barrett's type' mucosa seen?

YES NO

If NO, please state minimum length required .....

b) *Less than* 3cm of Barrett's mucosa seen?

YES NO

c) *Only* streaks or isolated mucosal islands seen

YES NO

d) *Only* areas of non-confluent areas of Barrett's type mucosa seen?

YES NO

2. Which of the following do you give a measurement for? :
Please tick the appropriate box

	YES	**NO**
GOJ		
SCJ		
Diaphragmatic hiatus level		
Length of BO seen		
Proximal extent of non-confluent BO		

3. Is the presence of oesophagitis always noted?

YES NO

If YES, is the proximal extent noted? Y N
Which grading system do you use?.....

Further comments
.....
.....

4. Are the following always noted?
Please tick the appropriate box

	YES	NO
Strictures		
Hiatus hernia		
Gastritis		
Duodenitis		

5. Biopsy practice

a) What proportion of patients with Barrett's Oesophagus do you biopsy at **first diagnostic endoscopy?**

ALL More than Half Less than Half

b) How many biopsies do you take? .....

c) What size forceps do you use? .....

d) What is the distance between biopsy sites (cm)?.....

6. Information stated *by you* on histology form :
Please tick the appropriate box

	YES	**NO**
Biopsy site (cm)		
Level of GOJ		
Presence of Hiatus hernia		

Further comments

.....
.....
.....
.....

7. Do you test for *Helicobacter Pylori* at diagnostic endoscopy?

YES NO

If YES what proportion of overall patients?

ALL More than Half Less than Half

What type of patient do you test for *H-pylori* on?
Please tick appropriate box

	YES	NO
All patients with BO?		
Patients with associated gastritis or duodenitis?		
Patients with associated gastric or duodenal ulcers?		

What method of detection do you use?

.....

8. Do you feel you have changed your practice over the last 5-10 years? (if applicable)

YES NO

If YES in which areas? Please comment

a) recognition of BO segment

YES NO

.....
.....

b) Length of BO present necessary for diagnosis

YES NO

.....
.....

c) biopsy technique/protocol

YES NO

Further comments :

.....
.....

Part C Surveillance

Please circle appropriate answers or write in space provided

1. Patients recalled for a repeat OGD
What proportion of patients with uncomplicated BO do you survey?

ALL More than Half Less than Half

If patients undergo a selective surveillance policy what criteria do you use?

a) Only people proven to have columnar lined oesophagus (**with or without intestinal metaplasia** on histology) surveyed

YES NO

b) Only people proven to have columnar lined oesophagus ***with*** **intestinal metaplasia** on histology surveyed?

YES NO

c) Other? Please comment

.....

.....

Surveillance Interval

Please tick box for most appropriate surveillance interval

	1 mnth or <	1-6 mnths	6 –12 mnths	1-3 years	5 years
BO diagnosed visually only (no histology)					
BO with CLO on histology but *no* IM					
BO with CLO + IM on histology					
BO with indefinite dysplasia on histology					
BO with LGD on histology					
BO with HGD on histology					

2. Surveillance biopsy technique
Please answer in the spaces provided

What type of forceps do you use?
.....

Number of biopsies *at each level*.....

Distance between biopsies (cm)
.....

Stains used.....
.

Please comment
.....
.....
.....
.....

3. What reasons for cessation of surveillance would you think reasonable?

a) 'stable' BO (ie. No worsening histology, no increase in segment length and no deterioration in symptoms)

YES NO

If YES, after how many years? .....years

b) age/mobility/quality of life issues in 'stable BO' patient

YES NO

c) not suitable for oesophagectomy if cancer diagnosed.

YES NO

Further comments
.....
.....END

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